In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

This study includes documents that were originally reported in a language other than English. All documents that are available in English have been made available via the GSK Clinical Study Register. Any additional documents that have not been translated to English may be made available, redacted in the original language, subject to an approved research proposal. For further information please see the Patient Level Data section of the GSK Clinical Study Register.

Final Study Report

Rota-006
(444563/006)

November 14, 2003

GlaxoSmithKline

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

CONFIDENTIAL

Final Study Report for Clinical Trial 444563/006 (rota-006)

Title: A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with HRV, when administered concurrently with DTPw-HBV and Hib vaccines.

Study vaccines:	GSK Biologicals' live attenuated human rotavirus vaccine.
CPMS Study No.:	444563/006 (rota-006)
Indication:	Two oral doses at two months interval to healthy infants, 2 months (6–12 weeks) of age at the time of Dose 1.
Principal Investigators:	Dr. [redacted] M.D., Brazil Dr. [redacted] M.D., Mexico Dra. [redacted] M.D., Venezuela Dra. [redacted] Ph.D as the Principal Study Co-ordinator for Venezuela
Date of First Visit:	May 25, 2001
Data Lock Point:	April 24, 2003
Coordinating Author:	[redacted] Scientific Writer
Contributing authors:	[redacted] Biometrician Director Central Study Coordinator Clinical Development Manager Biometrician

The trial was performed according to the Good Clinical Practice guidelines in operation at the time of the initiation of the trial.

Report Date: November 14, 2003

Verification and approval

I agree with the conclusions based on the data contained in this report

[redacted]

Dr. [redacted] **M.D.**

1/12/2003

Date (day/month/year)

GlaxoSmithKline

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

CONFIDENTIAL

Final Study Report for Clinical Trial 444563/006 (rota-006)

Title: A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with HRV, when administered concurrently with DTPw-HBV and Hib vaccines.

Study vaccines:	GSK Biologicals' live attenuated human rotavirus vaccine.
CPMS Study No.:	444563/006 (rota-006)
Indication:	Two oral doses at two months interval to healthy infants, 2 months (6-12 weeks) of age at the time of Dose 1.
Principal Investigators:	Dr [redacted] M.D., Brazil Dr [redacted] M.D., Mexico Dra [redacted] M.D., Venezuela Dra [redacted] Ph.D as the Principal Study Co-ordinator for Venezuela
Date of First Visit:	May 25, 2001
Data Lock Point:	April 24, 2003
Coordinating Author:	[redacted] Scientific Writer
Contributing authors:	[redacted] Biometrician [redacted] Director [redacted] Central Study Coordinator [redacted] Clinical Development Manager [redacted] Biometrician

The trial was performed according to the Good Clinical Practice guidelines in operation at the time of the initiation of the trial.

Report Date: November 14, 2003

Verification and approval

[redacted] based on the data contained in this report

[redacted]

Dr. [redacted] **M.D.** 18 / 12 / 2003 **Date (day/month/year)**

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

CONFIDENTIAL

Final Study Report for Clinical Trial 444563/006 (rota-006)

Title: A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with HRV, when administered concurrently with DTPw-HBV and Hib vaccines.

Study vaccines:	GSK Biologicals' live attenuated human rotavirus vaccine.
CPMS Study No.:	444563/006 (rota-006)
Indication:	Two oral doses at two months interval to healthy infants, 2 months (6–12 weeks) of age at the time of Dose 1.
Principal Investigators:	Dr. [redacted] M.D., Brazil Dr. [redacted] M.D., Mexico Dra. [redacted] M.D., Venezuela Dra. [redacted] Ph.D as the Principal Study Co-ordinator for Venezuela
Date of First Visit:	May 25, 2001
Data Lock Point:	April 24, 2003
Coordinating Author:	[redacted] Scientific Writer
Contributing authors:	[redacted] Biometrician [redacted] Director [redacted] Central Study Coordinator [redacted] Clinical Development Manager [redacted] Biometrician

The trial was performed according to the Good Clinical Practice guidelines in operation at the time of the initiation of the trial.

Report Date: November 14, 2003

Verification and approval

I agree with the conclusions based on the data contained in this report

[redacted]

Dra. [redacted] **M.D.,**

01 DEC 2003

Date (day/month/year)

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

CONFIDENTIAL

Final Study Report for Clinical Trial 444563/006 (rota-006)

Title: A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with HRV, when administered concurrently with DTPw-HBV and Hib vaccines.

Study vaccines:	GSK Biologicals' live attenuated human rotavirus vaccine.
CPMS Study No.:	444563/006 (rota-006)
Indication:	Two oral doses at two months interval to healthy infants, 2 months (6–12 weeks) of age at the time of Dose 1.
Principal Investigators:	Dr. [redacted] M.D., Brazil Dr. [redacted] M.D., Mexico Dra. [redacted] M.D., Venezuela Dra. [redacted] Ph.D as the Principal Study Co-ordinator for Venezuela
Date of First Visit:	May 25, 2001
Data Lock Point:	April 24, 2003
Coordinating Author:	[redacted] Scientific Writer
Contributing authors:	[redacted] Biometrician [redacted] Director [redacted] Central Study Coordinator [redacted] Clinical Development Manager [redacted] Biometrician

The trial was performed according to the Good Clinical Practice guidelines in operation at the time of the initiation of the trial.

Report Date: November 14, 2003

Verification and approval

I agree with the conclusions based on the data contained in this report

[redacted]

Dra. [redacted]

05 / 12 / 2003

Date (day/month/year)

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

CONFIDENTIAL

Final Study Report for Clinical Trial 444563/006 (rota-006)

Title: A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with HRV, when administered concurrently with DTPw-HBV and Hib vaccines.

Study vaccines:	GSK Biologicals' live attenuated human rotavirus vaccine.
CPMS Study No.:	444563/006 (rota-006)
Indication:	Two oral doses at two months interval to healthy infants, 2 months (6–12 weeks) of age at the time of Dose 1.
Principal Investigators:	Dr. [redacted] M.D., Brazil Dr. [redacted] M.D., Mexico Dra. [redacted] M.D., Venezuela Dra. [redacted] Ph.D as the Principal Study Co-ordinator for Venezuela
Date of First Visit:	May 25, 2001
Data Lock Point:	April 24, 2003
Coordinating Author:	[redacted] Scientific Writer
Contributing authors:	[redacted] Biometrician [redacted] Director [redacted] Central Study Coordinator [redacted] Clinical Development Manager [redacted] Biometrician

The trial was performed according to the Good Clinical Practice guidelines in operation at the time of the initiation of the trial.

Report Date: November 14, 2003

Synopsis of Final Report for Clinical Trial 444563/006 (rota-006)

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Title of the study: A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ foci forming units (ffu)) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with HRV, when administered concurrently with DTPw-HBV and Hib vaccines.

Principal Investigators: Dr. [redacted] M.D., Brazil
Dr. [redacted] M.D., Mexico
Dra. [redacted] M.D., Venezuela
Dra. [redacted] Ph.D as the Principal Study Co-ordinator for Venezuela

Study sites: This multicentre trial was conducted in Brazil, Mexico and Venezuela.

Publications:

- Protective efficacy of an oral HRV vaccine in Latin American infants. Poster presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Diego, USA, September 27–30, 2002.
- Immunogenicity and reactogenicity of an oral HRV vaccine in Latin American infants. Poster presented at the World Society for Pediatric Infectious Diseases (WSPID), Santiago, Chile, November 18–21, 2002.
- Impact of maternal antibodies on the immune response to an oral human rotavirus (HRV) vaccine in Mexican infants. Poster presented at the WSPID, Santiago, Chile, November 18–21, 2002.
- Efficacy of two doses of a human monovalent rotavirus vaccine, Rotarix®, in preventing gastro-enteritis due to G1 and non-G1 rotavirus in Brazil, Mexico and Venezuela. Oral communication at the 8th International Symposium on DS-RNA Viruses, Lucca, Italy, September 13–18, 2003.

Study period: Date of first visit: May 25, 2001 Data lock point: April 24, 2003	**Clinical phase:** IIb

Note: Although all study objectives and endpoints are listed, this study report only presents the efficacy, safety and immunogenicity obtained during the first efficacy follow-up period. An annex report will present results obtained during the second efficacy follow-up period.

Objectives: Primary:

For the subset of subjects who were planned to receive two doses of HRV or placebo:

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine, to demonstrate the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations in preventing any rotavirus (RV) gastroenteritis (GE) during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period.

Secondary:

First efficacy follow-up period

For the subset of subjects planned to receive two doses of HRV or placebo:

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

vaccine, to assess if two doses of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations can:

- Prevent severe RV GE during-the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Prevent RV GE due to virus types heterologous to vaccine strain from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Prevent any and severe pure RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Prevent mixed RV GE (GE associated with RV and at least one other pathogen) during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Prevent any hospitalization for RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.

For the subset of subjects who received three dose of HRV or placebo:

- To explore the rates of any and severe RV GE during the period starting from 2 weeks after Dose 3 until the end of the first efficacy follow-up period.

Second efficacy follow-up period (for a subset of approximately 1000 subjects)

- To evaluate the efficacy of the HRV vaccine during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period, and during the period starting from 2 weeks after the last HRV/placebo dose until the end of the second efficacy follow-up period.

Safety/Reactogenicity

- To assess the safety and reactogenicity of two doses of GSK Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo.
- To assess the safety and reactogenicity of the third dose of GSK Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo in a subset of subjects.

Immunogenicity

For the subset of subjects who were planned to receive two doses of HRV or placebo:

- To assess vaccine take, in subjects previously uninfected with RV before vaccination, two months after each study vaccine dose in the stool analysis subset (subjects with at least one available result for stools collected at pre-determined timepoints). Vaccine take was defined as the appearance of serum IgA to RV in post-immunization sera at a concentration ≥ 20 U/ml and/or vaccine virus shedding in any stool sample collected from Visit 1 to Visit 3.
- To assess persistence of serum IgA to RV at the end of the first efficacy follow-up period.
- To explore in a subset of subjects effect of GSK Biologicals' HRV vaccine on the immune response to concurrently administered routine vaccinations.
- To explore the effect of unrestricted feeding on the immunogenicity of the vaccine.
- To assess viral shedding in the vaccine groups in the stool analysis subset.

For the subset of subjects who received three doses of HRV or placebo:

- To assess serum IgA to RV, two months after Dose 2 and Dose 3 of HRV vaccine or placebo.
- To assess viral shedding in the vaccine groups after the third HRV vaccine dose.
- To explore the effect of GSK Biologicals' HRV vaccine on the immune response to concurrently administered routine vaccinations two months after the third dose of routine vaccines.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Methodology:
Study design: Double-blind, randomized, placebo-controlled study with four parallel groups with balanced allocation (1:1:1:1). Two oral doses were administered according to a 0, 2 month schedule to healthy infants who were 2 months of age at the time of Dose 1 of HRV vaccine or placebo. A subset of subjects received a third dose of the HRV vaccine or placebo at 6 months of age. No restrictions on feeding the infants before or after study vaccine or placebo administration. Hepatitis B, Bacillus Calmette-Guerin (BCG) and oral polio vaccine (OPV) vaccinations at birth were allowed according to local Expanded Program of Immunization (EPI). For the subset planned to receive two doses of HRV vaccine or placebo, routine vaccinations [diphtheria-tetanus-whole-cell pertussis-hepatitis B-*Haemophilus influenzae* type b vaccine (DTPw-HB+Hib vaccine)] were to be administered concomitantly with the study vaccines at 2 and 4 months of age; thereafter, DTPw-HB+Hib vaccine was to be given at 6 months of age. Subjects planned to receive three doses of HRV vaccine or placebo were to receive the routine vaccinations concomitantly with each dose of HRV vaccine or placebo. OPV was to be given at the discretion of the investigator, but was not to be administered during the period starting 2 weeks before each dose of study vaccine and ending 2 weeks after.

Number of subjects:

Planned study enrolment: 2640 **Amended target enrolment:** 2276
Total number of subjects enrolled: 2276 **Completed Visit 4:** 2125

Subset planned to receive two doses of HRV vaccine or placebo

Enrolled: 2155 Completed Visit 4: 2004 (Of the 151 drop outs, 3 were due to unrelated Serious Adverse Events (SAEs) and 6 were due to non-serious adverse events (AEs))

Analyzed for efficacy during the 1st efficacy follow-up period:

Total vaccinated cohort: 2044 subjects (507 in $10^{4.7}$ ffu HRV group, 508 in $10^{5.2}$ ffu HRV group, 512 in $10^{5.8}$ ffu HRV group and 517 in placebo group)

According to protocol (ATP) cohort: 1846 subjects (468 in $10^{4.7}$ ffu HRV group, 460 in $10^{5.2}$ ffu HRV group, 464 in $10^{5.8}$ ffu HRV group and 454 in placebo group)

Analyzed for safety:

Total vaccinated cohort: 2155 subjects (538 in $10^{4.7}$ ffu HRV group, 540 in $10^{5.2}$ ffu HRV group, 540 in $10^{5.8}$ ffu HRV group and 537 in placebo group)

ATP cohort: 1965 subjects (499 in $10^{4.7}$ ffu HRV group, 487 in $10^{5.2}$ ffu HRV group, 493 in $10^{5.8}$ ffu HRV group and 486 in placebo group).

Analyzed for immunogenicity:

Total vaccinated cohort: 2151 subjects (537 in $10^{4.7}$ ffu HRV group, 535 in $10^{5.2}$ ffu HRV group, 540 in $10^{5.8}$ ffu HRV group and 539 in placebo group).

ATP cohort: 1526 subjects (395 in $10^{4.7}$ ffu HRV group, 377 in $10^{5.2}$ ffu HRV group, 381 in $10^{5.8}$ ffu HRV group and 373 in placebo group).

Subset receiving three doses of HRV vaccine or placebo

Enrolled and included in the total vaccinated cohort for analysis of efficacy, safety and immunogenicity: 121 Completed Visit 4: 121

Diagnosis and criteria for inclusion: Healthy infants, born after a normal gestation period of 36–42 weeks or with a birth weight > 2000 g, 6–12 weeks of age at the time of the first dose of HRV vaccine or placebo, free of obvious health problems as established by medical history and clinical examination before entering into the study, and with written informed consent obtained from parents or guardians of the subject.

CARS Id : **CLIN_200310_17566**/ Version : **1.7,Admin. QC**/ Modify Date : **15/11/2003**

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Test product, dose, mode of administration, lot numbers:

- One dose of GSK Biologicals' lyophilized HRV vaccine contained $10^{4.7}$ ffu, $10^{5.2}$ ffu or $10^{5.8}$ ffu of HRV strain, RIX4414 derived from the 89-12 HRV vaccine strain, 9 mg sucrose, 18 mg dextran, 13.5 mg sorbitol and 9 mg amino acids. Lot numbers: DRVC005A46 for HRV vaccine $10^{4.7}$ ffu, DRVC010A48 for HRV vaccine $10^{5.2}$ ffu and DRVC004A46 for HRV vaccine $10^{5.8}$ ffu. Lot numbers 00J03/1010, 00I19/1006, 00J03/1010, 00J04/1011 and 01C09/1013 were used for the diluent (calcium carbonate 60 mg/ml and xanthane 0.25 % in 1 ml water for injection).

Mode of administration: Lyophilized HRV vaccine was reconstituted with the supplied diluent and the resuspended product was administered as a single oral dose.

Reference therapy, dose and mode of administration, lot numbers:

- One dose of GSK Biologicals' lyophilized placebo for HRV vaccine contained 9 mg sucrose, 18 mg dextran, 13.5 mg sorbitol and 9 mg amino acids. Lot numbers: DRVC014A48PL and DRVC006A46PL.
  Lot numbers 00J03/1010, 00I19/1006, 00J03/1010, 00J04/1011 and 01C09/1013 were used for the diluent (calcium carbonate 60 mg/ml and xanthane 0.25 % in 1 ml water for injection).

Mode of administration: Lyophilized placebo was reconstituted with the supplied diluent and the resuspended product was administered as a single oral dose.

Duration of study: For the subjects who participated only in the first efficacy follow-up period (until age 12 months), the intended duration of the study, per subject, was approximately 10 months. For the subset of subjects who participated in a second efficacy follow-up period (until maximum age 24 months), the intended duration of the study, per subject, was 22 months at most.

Criteria for evaluation:

Efficacy: Recording of rectal/axillary temperature, number of vomiting episodes, number of looser than normal stools passed by the subject, treatment administered and any dehydration during each suspected episode of GE (defined as diarrhea) occurring during the study.

Collection of stool samples during each diarrheal episode for RV detection by Enzyme Linked Immunosorbent Assay (ELISA). RV type was determined by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR). Episodes were counted as distinct events only if there were 5 or more symptom-free days between the episodes. A 20-point scoring system was used to assess the severity of each GE episode (Ruuska T and Vesikari T, Scand J Infect Dis 1990;22:259–67). A score of < 7 was prospectively defined as mild, a score of 7–10 was prospectively defined as moderate and a score ≥ 11 was prospectively defined as severe (Joensuu J *et al*, Lancet 1997;350:1205–9).

***Primary endpoint*:**

For the subset of subjects planned to receive two doses of HRV or placebo:

- Occurrence of any RV GE during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period.

Secondary endpoints:

For the subset of subjects who received two doses of HRV or placebo:

- Occurrence of severe RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of RV GE due to virus types heterologous to vaccine strain during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of any and severe pure RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

- Occurrence of RV GE in which there is at least one other pathogen during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of hospitalization for RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.

For the subset of subjects who received three doses of HRV or placebo:

- Occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 3 until the end of the first efficacy follow-up period.

For the subset of subjects who participated in the second efficacy follow-up period until maximum age 24 months:

- For the subset of subjects who received two doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.
- For the subset of subjects who received two doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the second efficacy follow-up period.
- For the subset of subjects who received three doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.
- For the subset of subjects who received three doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 3 until the end of the second efficacy follow-up period.

Reactogenicity and safety: Recording of solicited symptoms (cough/runny nose, diarrhea, fever, fussiness/irritability, loss of appetite and vomiting) during the 15-day follow-up period (Day 0 to Day 14) after each study vaccination. Recording of unsolicited symptoms during the 43-day follow-up period (Day 0 to Day 42) after each study vaccination and SAEs during the entire study period.

***Secondary endpoints*:**

- For each type of solicited symptoms, occurrence of the symptom within the 15-day solicited follow-up period after any dose of study vaccine (in a subset after Dose 3).
- Occurrence of unsolicited symptoms within 43 days (Day 0 to Day 42) after Dose 1, Dose 2 (in all subjects) and Dose 3 (in a subset) of study vaccination, according to World Health Organization (WHO) classification.
- Occurrence of SAEs throughout the entire study period.

Immunogenicity:

For the subset of subjects planned to receive two doses of HRV or placebo:

Measurement of serum concentration of anti-rotavirus IgA antibodies before Dose 1 (all subjects), two months after Dose 1 (in a subset of subjects), two months after Dose 2 (in a subset of subjects) and at the end of the first efficacy follow-up period (all subjects).

Detection of RV in stool samples (shedding) collected on the day of Dose 1 and Dose 2 and on Day 7±1 after Dose 1 and Dose 2 in the stool analysis subset.

Measurement of serum concentration of antibodies to routine vaccinations (DTPw-HB+Hib and OPV) two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period in a subset of subjects.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

For the subset of subjects who received three doses of HRV or placebo:
Measurement of serum concentration of anti-rotavirus IgA antibodies at Visit 1, two months after Dose 2 and two months after Dose 3 in all subjects from this subset.
Detection of RV (shedding) in stool samples collected on the day of Dose 3 and on Day 7±1 after Dose 3 from all subjects from this subset.
Measurement of serum concentration of antibodies to routine vaccinations (DTPw-HB+Hib and OPV) two months after Dose 2 and two months after Dose 3 of HRV vaccine or placebo in all subjects from this subset.

***Secondary endpoints*:**
For the subset of subjects planned to receive two doses of HRV or placebo:

- Serum rotavirus IgA antibody titers at Visit 1 and the end of the first efficacy follow-up period in all subjects and at Visits 2 and 3 in a subset of subjects.
- Proportion of subjects with vaccine take at Visits 2 and 3 in the stool analysis subset.
- Vaccine take and Geometric Mean Concentration (GMCs) of RV IgA ELISA will be calculated in a subset for breast-fed infants compared with formula fed infants for the following 3 categories: 1) whether the infant received no food 1 hour prior to and 30 minutes after Dose 1 or Dose 2 (as reported by the mother); 2) whether the infant received food 1 hour prior to Dose 1 or Dose 2 (as reported by the mother); and 3) whether the infant received food within 30 minutes after Dose 1 or Dose 2.
- Viral shedding in the vaccine groups in the stool analysis subset.

Two months after Dose 2 (at Visit 3) and at the end of the first efficacy follow-up period in a subset of subjects:

- GMC/Ts for anti-PRP, anti-diphtheria, anti-tetanus, anti-BPT, anti-poliovirus types 1, 2 and 3, and anti-HBs antibodies.
- Seroprotection status:
  - anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml.
  - anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml.
  - anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml.
  - anti-HBs antibody concentrations ≥ 10 mIU/ml.
  - anti-poliovirus type 1 antibody titers ≥ 8.
  - anti-poliovirus type 2 antibody titers ≥ 8.
  - anti-poliovirus type 3 antibody titers ≥ 8.
- Seropositivity status:
  - anti-BPT antibody concentrations ≥ 15 EL.U/ml.

For the subset of subjects who received three doses of HRV or placebo:

- Serum anti-rotavirus IgA antibody concentrations at Visits 1, 3 and 4.
- GMC/Ts for anti-PRP, anti-diphtheria, anti-tetanus, anti-BPT, anti-poliovirus types 1, 2 and 3, and anti-HBs antibodies two months after Dose 3.
- Seroprotection status two months after Dose 3:
  - anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml.
  - anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml.
  - anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml.
  - anti-HBs antibody concentrations ≥ 10 mIU/ml.
  - anti-poliovirus type 1 antibody titers ≥ 8.
  - anti-poliovirus type 2 antibody titers ≥ 8.
  - anti-poliovirus type 3 antibody titers ≥ 8.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

- Seropositivity status two months after Dose 3:
  - anti-BPT antibody concentrations ≥ 15 EL.U/ml
- Viral shedding in the vaccine groups on the day of and on Day 7 after Dose 3.

Statistical methods:

Efficacy:

Primary efficacy analysis for the subset planned to receive two doses of HRV or placebo was performed on the According to Protocol (ATP) cohort.

The duration of the efficacy follow-up period was summarized by group. The percentages of subjects with RV GE (overall, by RV type and by country) of any and severe intensity from 2 weeks after Dose 2 until the end of the first efficacy follow-up period were calculated with their 95% Confidence Interval (CI). The percentages of subjects hospitalized due to RV GE from 2 weeks after Dose 2 until the end of the first efficacy follow-up period were also calculated with their 95% CI. Two-sided Fisher's exact test (significance level of $\alpha = 0.05$) was used to compare these percentages between group.

The efficacy rate (overall, by RV type and by country) of the pooled HRV vaccine groups and each HRV vaccine group relative to the placebo was calculated with its 95% CI against RV GE (any and severe intensity) occurring from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The efficacy rate with its 95% CI was also calculated against hospitalization due to RV GE occurring from 2 weeks after Dose 2 until the end of the first efficacy follow-up period.

Safety and reactogenicity:

Primary analysis of safety and reactogenicity was performed on the total vaccinated cohort. The percentages of doses and of subjects with any symptom (solicited or unsolicited), with specific solicited symptoms reported during the 15-day follow-up period and with unsolicited symptoms classified by WHO Preferred Term reported during the 43-day follow-up period were tabulated with their exact 95% CI. The same calculations were done for symptoms rated as grade "2 or 3" (only for solicited symptoms), those rated as grade "3" in intensity and for those assessed as related to vaccination. Pair-wise differences among the three HRV vaccine groups and between the pooled HRV vaccine group and the placebo group were explored using the two-sided Fisher's exact test for the reactogenicity endpoints, only for the subset of subjects planned to receive two doses of HRV vaccine or placebo. SAEs and discontinuations due to SAEs or non-serious adverse events (AEs) were described.

Immunogenicity:

Primary immunogenicity analysis for the subset planned to receive two doses of HRV or placebo was performed on the ATP cohort. Geometric Mean Concentration/Titer (GMC/T) and seroconversion/seroprotection/seropositivity rates were calculated with their 95% CI for each antibody measured at each blood sampling time point. The percentage of subjects with presence of RV in stool samples collected at Day 0 and Day 7 of each study vaccination was calculated for the stool analysis subset. The proportion of subjects in the stool analysis subset with vaccine take after each dose of HRV vaccine, and after combined doses 1 and 2 were tabulated with their exact 95% CI. Asymptotic standardized two-sided 95% CIs were calculated for difference in vaccine take on combined doses at Visit 3 between each HRV vaccine group and the placebo group.

Differences between each HRV vaccine group and placebo and between the pooled HRV vaccine group and the placebo group with respect to immune response to concomitant vaccination at two months after Dose 2 of HRV vaccine or placebo and at the end of first efficacy follow up period were explored.

Results for the subset planned to receive two doses of HRV vaccine or placebo:

444563/006 Synopsis page 7 of 12

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Demographic results: The mean age of the total vaccinated cohort at the time of the first study vaccine dose was 8.3 weeks (range 6–12 weeks). The demographic profile of the four groups was similar with respect to mean age, mean height and mean weight at the time of Dose 1 of HRV vaccine or placebo and race distribution. Slight differences in gender distribution were observed.

Efficacy results:
The first efficacy follow-up period started from two weeks after Dose 2 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age).
Primary endpoint: A statistically significant decrease in the percentage of subjects reporting any RV GE during the first efficacy follow-up period was detected in the pooled HRV vaccine group and in each HRV vaccine group as compared to the placebo group ($p < 0.05$, two-sided Fisher's exact test).
The efficacy of the vaccine against any RV GE during the first efficacy follow-up period (ATP cohort for efficacy analysis) was as follows:

Group	N	Rate			Vaccine Efficacy			p-value
		%	95% CI		%	95% CI		
			LL	UL		LL	UL	
HRV$10^{4.7}$ ffu	468	4.5	2.8	6.8	58.4	29.4	76.3	<0.001
HRV $10^{5.2}$ ffu	460	4.8	3.0	7.2	55.7	25.3	74.5	<0.001
HRV $10^{5.8}$ ffu	464	3.2	1.8	5.3	70.0	45.7	84.4	<0.001
Pooled HRV	1392	4.2	3.2	5.4	61.4	42.3	74.1	<0.001
Placebo	454	10.8	8.1	14.0	-	-	-	-

N = number of subjects included in each group; 95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Rate = percentage of subjects reporting at least one RV GE episode in each group
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Secondary endpoints (ATP cohort for efficacy analysis):
- During the first efficacy follow-up period, a statistically significant decrease ($p < 0.05$, two-sided Fisher's exact test) in the percentage of infants with severe RV GE and hospitalizations due to RV GE was detected in pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group.
- A statistically significant decrease (p-value < 0.05, two-sided Fisher's exact test) in the percentage of infants with any/severe RV GE caused by G1 type was detected in pooled HRV vaccine group as compared to the placebo group.
- A statistically significant decrease (p-value < 0.05, two-sided Fisher's exact test) in the percentage of infants with any/severe RV GE caused by non-G1 types (either G2, G3, G4 or G9 type) was detected in pooled HRV vaccine groups as compared to the placebo group indicating cross-protection with GSK Biologicals' HRV vaccine.
- Efficacy estimates against pure and mixed RV GE were not calculated since concurrent pathogens were not identified in the majority of RV GE episodes.

Reactogenicity and safety results:
- Incidences of symptoms (solicited or unsolicited) reported within 15 days after vaccination, including those rated as grade "3" and those assessed as related, were similar between the groups.
- Incidences of solicited symptoms, including those rated as grade "2 or 3", those rated as grade "3" and those assessed as related to vaccination, reported within 15 days after vaccination were similar between the groups. There was no increase in reactogenicity from Dose 1 to Dose 2 of HRV vaccine or placebo or with increasing viral concentration.
- Percentages of subjects reporting solicited symptoms during the 15-day follow-up period after any dose of HRV vaccine or placebo (total vaccinated cohort for safety analysis) in subset planned to receive two doses of HRV vaccine or placebo were as follows:

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

		HRV $10^{4.7}$ ffu N = 538			HRV $10^{5.2}$ ffu N = 540			HRV $10^{5.8}$ ffu N = 540			Placebo N = 537		
Symptom		**%**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**
Cough/ runny nose	Total	78.1	74.3	81.5	77.8	74.0	81.2	78.3	74.6	81.7	81.4	77.8	84.6
	Grade 3	16.4	13.3	19.8	16.9	13.8	20.3	17.0	14.0	20.5	13.2	10.5	16.4
	Related	29.2	25.4	33.2	31.1	27.2	35.2	30.4	26.5	34.4	30.2	26.3	34.2
Diarrhea	Total	12.6	10.0	15.7	11.3	8.8	14.3	14.3	11.4	17.5	15.8	12.8	19.2
	Grade 3	3.0	1.7	4.8	4.3	2.7	6.3	4.3	2.7	6.3	4.3	2.7	6.4
	Related	6.5	4.6	8.9	7.6	5.5	10.2	8.3	6.1	11.0	7.6	5.5	10.2
Irritability/ fussiness	Total	78.4	74.7	81.8	80.7	77.2	84.0	81.7	78.1	84.8	82.7	79.2	85.8
	Grade 3	18.0	14.9	21.5	18.0	14.8	21.5	17.6	14.5	21.1	20.3	17.0	24.0
	Related	47.2	42.9	51.5	46.7	42.4	51.0	49.4	45.1	53.7	48.0	43.7	52.4
Loss of appetite	Total	44.6	40.4	48.9	45.6	41.3	49.9	44.6	40.4	48.9	46.9	42.6	51.2
	Grade 3	3.3	2.0	5.2	3.9	2.4	5.9	2.8	1.6	4.5	3.7	2.3	5.7
	Related	20.3	16.9	23.9	20.0	16.7	23.6	19.3	16.0	22.8	22.0	18.5	25.7
Fever	Total	76.2	72.4	79.7	78.1	74.4	81.6	75.2	71.3	78.8	79.1	75.5	82.5
	Grade 3	2.8	1.6	4.6	3.7	2.3	5.7	3.9	2.4	5.9	3.9	2.4	5.9
	Related	43.9	39.6	48.2	41.3	37.1	45.6	41.5	37.3	45.8	41.7	37.5	46.0
Vomiting	Total	22.7	19.2	26.5	27.4	23.7	31.4	24.6	21.1	28.5	24.0	20.5	27.9
	Grade 3	4.5	2.9	6.6	8.1	6.0	10.8	7.2	5.2	9.7	5.0	3.3	7.2
	Related	12.6	10.0	15.7	13.0	10.2	16.1	10.4	7.9	13.3	13.0	10.3	16.2

N = total number of subjects having received at least one dose of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI: exact 95% Confidence Interval, LL = Lower Limit, UL = Upper Limit

- The incidences of the unsolicited symptoms including those rated as grade "3" in intensity or assessed as related to vaccination were similar between the groups.
- Six subjects planned to receive two doses of HRV vaccine or placebo dropped out due to non-serious AEs. Of these, one subject had a vaccination-related AE (grade 2 allergic reaction starting on the day of Dose 1 of study vaccine and concomitant DTPw-HB+Hib vaccine).
- Among the subjects planned to receive two doses of HRV vaccine or placebo, 220 subjects (52 in the $10^{4.7}$ ffu HRV vaccine group, 55 in the $10^{5.2}$ ffu HRV vaccine group, 49 in the $10^{5.8}$ ffu HRV vaccine group and 64 in the placebo group) reported at least one SAE until the end of the first efficacy follow-up period
- All SAEs reported until the end of the first efficacy follow-up period among the subjects planned to receive two doses of HRV vaccine or placebo were assessed as not related to study vaccination (HRV vaccine or placebo) by the respective investigators.
- Three subjects from the subset planned to receive two doses of HRV vaccine or placebo died due to unrelated SAEs during the course of the study.
- One SAE in the subset planned to receive two doses of study vaccine (bronchitis in the $10^{4.7}$ ffu HRV vaccine group) was assessed as possibly related to concomitantly administered routine vaccination (DTPw-HB+Hib) by the investigator.
- One case of intussusception (IS), assessed as not related to vaccination by the investigator, was reported in the subset planned to receive two doses of HRV vaccine or placebo. IS occurred in a 10-month old boy from Mexico, approximately 6 months after the 2nd dose of $10^{4.7}$ ffu HRV vaccine and concomitantly administered routine DTPw-HB+Hib vaccine.
- One SAE in the subset receiving three doses of study vaccine (pneumonia in the placebo group) was assessed as possibly related to the study vaccination by the investigator.

444563/006 Synopsis page 9 of 12

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Immunogenicity Results: Anti-rotavirus IgA antibody seroconversion rates, GMCs and vaccine take in a subset of subjects two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity analysis) were as follows:

Group	Seroconversion rate at PII(M4)				GMC (U/ml) at PII(M4)				Vaccine take at PII(M4) on combined Doses 1 and 2			
			95% CI				95% CI				95% CI	
	N	%	L.L	U.L	N	Value	L.L	U.L	N	%	L.L	U.L
HRV $10^{4.7}$	142	60.6	52.0	68.7	142	54.0	40.9	71.2	107	64.5	54.6	73.5
HRV $10^{5.2}$	125	62.4	53.3	70.9	125	52.1	39.7	68.3	109	72.5	63.1	80.6
HRV $10^{5.8}$	124	65.3	56.3	73.6	124	70.7	51.9	96.3	106	75.5	66.2	83.3
Placebo	132	5.3	2.2	10.6	132	<20.0	-	-	99	4.0	1.1	10.0

N = number of subjects with available results
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
95% CI: 95% Confidence Interval, LL = Lower Limit, UL = Upper Limit
Seroconversion rate = % with anti-rotavirus IgA antibody concentration ≥ 20 U/ml in subjects initially (i.e. prior to the first dose) negative for RV
Antibody concentration below the cut-off were given an arbitrary value of half the cut-off for GMC calculation
Vaccine take was measured only in the stool analysis subset

The percentages of subjects with RV shedding at Day 7 after Dose 1 ranged from 35.2% to 44.1% between the HRV vaccine groups. There was no shedding on the day of Dose 2 (approximately 2 months after Dose 1), except in one subject in $10^{5.8}$ ffu HRV vaccine group. The percentages of subjects with RV shedding at Day 7 after Dose 2 ranged from 11.5% to 21.3% between the HRV vaccine groups.

Antibody responses to all routine vaccine antigens (D, T, BPT, HBs, PRP, and poliovirus types 1, 2 and 3) at two months after Dose 2 of HRV vaccine or placebo in the three HRV vaccine groups were similar to those of the placebo (control) indicating that there appeared to be no impact of HRV vaccine on immunogenicity of OPV and concomitantly administered DTPw-HB+Hib vaccine, except for anti-diphtheria antibodies. There was a trend towards lower anti-diphtheria antibody seroprotection rates in the $10^{4.7}$ ffu and $10^{5.2}$ ffu HRV vaccine groups as compared to the placebo group at two months after Dose 2 of HRV vaccine or placebo. Persistence data for antibodies to all routine vaccine antigens at end of the first efficacy follow-up period in the three HRV vaccine groups were similar to those of the placebo (control) indicating that there was no apparent effect of the HRV vaccine on the immunogenicity of routine vaccines after completion of the three-dose primary vaccination course of routine vaccines.

Conclusions:
Study rota-006 demonstrated that two doses of GSK Biologicals' HRV vaccine were well tolerated, immunogenic and efficacious in protecting susceptible infants until approximately one year of age against RV GE in the Latin American setting where G1 and non-G1 RV serotypes were circulating. The highest viral concentration ($10^{5.8}$ ffu) evaluated showed higher immunogenicity and protection without increased reactogenicity.

Efficacy

- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups and each viral concentration) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of any RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The observed vaccine efficacy ranged between 55.7% to 70%. Thus, the primary objective of the study was met.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups and each viral concentration) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of severe RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The observed vaccine efficacy ranged between 65.8% to 85.6%.
- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of hospitalization due to RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The observed vaccine efficacy in pooled HRV vaccine groups was 79%.
- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of any and severe RV GE caused by G1 and non-G1 serotypes relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. Proof of concept that GSK Biologicals' monovalent G1[P8] HRV vaccine exhibits clinical protection against homotypic and heterotypic strains was thus demonstrated in the Latin American setting where G1 and non-G1 serotypes were circulating.
- The highest viral concentration of GSK Biologicals' HRV vaccine evaluated, $10^{5.8}$ ffu, consistently performed better in terms of homotypic and heterotypic protection against any and severe RV GE.

Safety/Reactogenicity

- The safety and reactogenicity profile of two doses of each viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations was similar to that of the placebo in terms of the incidences of solicited/unsolicited symptoms and SAEs reported after vaccination. There was no increase in reactogenicity with the use of higher viral concentration and from Dose 1 to Dose 2.
- Even the highest viral concentration used, HRV vaccine at $10^{5.8}$ ffu, did not result in increased reactogenicity as compared to placebo, confirming the mild reactogenicity profile of GSK Biologicals' attenuated HRV vaccine.

Immunogenicity

- Vaccine take rates ranged from 48.6% to 57.4% at two months after the first dose of GSK Biologicals' HRV vaccine containing $10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu. Vaccine take rates ranged from 62.6% to 69.1% at two months after the second dose.
- Persistence in terms of serum anti-rotavirus IgA antibodies at the end of the first efficacy follow-up period (approximately 8 months after the second dose) was similar for the three viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine.
- RV shedding was observed predominantly after Dose 1 of GSK Biologicals' HRV vaccine with little residual shedding two months after Dose 1.
- There was a trend towards higher immunogenicity in terms of IgA seroconversion rates, GMCs and vaccine take in the $10^{5.8}$ ffu HRV vaccine group at two months after Dose 2.
- The effect of unrestricted feeding on the immunogenicity of the HRV vaccine was evaluated and indicated that none of the pre-defined feeding criteria had a significant effect.
- GSK Biologicals' HRV vaccine did not appear to impact on immunogenicity of routine vaccines, DTPw-HB and Hib (given concomitantly) or OPV vaccine.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**
Exploratory evaluation of three doses of HRV vaccine in a subset of subjects • Within the limits of the small sample size, three doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups and each viral concentration) given concomitantly to healthy infants with routine vaccinations appeared to decrease the incidence of any and severe RV GE relative to the placebo during the period starting from 2 weeks after Dose 3 until the end of the first efficacy follow-up period. • The safety and reactogenicity profile of the three doses of each viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations was similar to that of the placebo in terms of the incidences of solicited/unsolicited symptoms and SAEs reported after vaccination. • Anti-rotavirus IgA antibody responses in terms of seropositivity and GMCs were similar for the three viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) at two months after the second dose and at two months after the third dose of GSK Biologicals' HRV vaccine. There was a trend towards higher immunogenicity in the $10^{5.8}$ ffu HRV vaccine group. • RV shedding observed after the third dose of GSK Biologicals' HRV vaccine was similar for the three viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu). • GSK Biologicals' HRV vaccine did not appear to impact on immunogenicity of routine vaccines, DTPw-HB and Hib (given concomitantly) or OPV vaccine.		
Date of report: November 14, 2003		
444563/006 Synopsis page 12 of 12		

CONTENTS: TEXT

Synopsis of Final Report for Clinical Trial 444563/006 (rota-006) ***2***

1 Introduction/Rationale ***29***

2 Study Objectives ***30***

2.1 Primary objective **30**

2.2 Secondary objectives **31**

3 Methodology ***33***

3.1 Study design **33**

3.2 Investigators and trial centres **35**

3.3 Ethics **36**
3.3.1 Protocol amendments/modifications 37

3.4 Selection of study population **39**
3.4.1 Inclusion criteria 39
3.4.2 Exclusion criteria 39
3.4.3 Elimination criteria during the study up to Visit 3 (up to Visit 4 for the subset of subjects receiving three doses of study vaccine or placebo) 40
3.4.4 Elimination criteria during the study from Visit 3 (from Visit 4 for the subset of subjects receiving three doses of study vaccine or placebo) until study end 41
3.4.5 Contraindications to vaccination 41

3.5 Study vaccines and administration **42**
3.5.1 GSK Biologicals' HRV vaccine 43
3.5.2 GSK Biologicals' placebo for HRV vaccine 43
3.5.3 GSK Biologicals' calcium carbonate buffer used as diluent 43
3.5.4 Dosage and administration 43

3.6 Routine vaccines and administration **44**
3.6.1 GSK Biologicals' DTPw-HB+Hib vaccine 44
3.6.2 GSK Biologicals' OPV (Polio Sabin) vaccine 45
3.6.3 Dosage and administration 45

3.7 Treatment allocation and randomization **45**
3.7.1 Randomization of supplies 45
3.7.2 Randomization of subjects 46
3.7.3 Subset definition 46

3.8 Blinding **47**

3.9 Study procedures **48**

3.10 Subject completion and drop out **49**

3.11 Assessment of efficacy variables **50**
3.11.1 Diarrheal stool analysis 53

3.12 Assessment of safety variables **53**
3.12.1 Pregnancy 57
3.12.2 Prior and concomitant medication 57

3.13 Assessment of immunogenicity variables **58**
3.13.1 Intervals between study visits 58
3.13.2 Laboratory assays and timepoints 59
3.13.2.1 Stool analysis 59

3.13.2.2 Serum analysis ... 60

3.14 Data quality assurance ... 61

3.15 Statistical methods ... 62
3.15.1 Primary endpoint ... 62
3.15.2 Secondary endpoints ... 63
3.15.3 Determination of sample size ... 65
3.15.4 Study cohorts/data sets analyzed ... 68
3.15.5 Analysis of demographics ... 70
3.15.5.1 For the subset planned to receive two doses of HRV vaccine or placebo ... 70
3.15.5.2 For the subset receiving three doses of HRV vaccine or placebo ... 70
3.15.6 Analysis of efficacy ... 71
3.15.6.1 Efficacy during first efficacy follow-up period for the subset planned to receive two doses of HRV vaccine or placebo ... 71
3.15.6.2 Exploratory efficacy during the first efficacy follow-up period for the subset receiving three doses of HRV vaccine or placebo ... 73
3.15.7 Analysis of safety ... 73
3.15.7.1 Reactogenicity of two doses of HRV vaccine and placebo ... 73
3.15.7.2 Reactogenicity of HRV vaccine and placebo in the subset receiving three doses of HRV vaccine or placebo ... 75
3.15.8 Analysis of immunogenicity ... 76
3.15.8.1 Immunogenicity of the HRV vaccine for the subset planned to receive two doses of HRV vaccine or placebo ... 76
3.15.8.2 Immunogenicity of routine DTPw-HBV+Hib and OPV vaccines for the subset receiving two doses of HRV vaccine or placebo ... 79
3.15.8.3 Immunogenicity analysis for the subset receiving three doses of HRV vaccine or placebo ... 80

3.16 Interim analyses ... 81

3.17 Annex analyses ... 82

3.18 Changes in conduct of the study/planned analyses ... 82

4 Study population planned to receive two doses of HRV vaccine or placebo ... 83

4.1 Study dates ... 83

4.2 Subject eligibility and attrition from study ... 83
4.2.1 Number and distribution of subjects ... 83
4.2.2 Study completion and drop out ... 84
4.2.3 Eligibility for analysis ... 86
4.2.4 Compliance with protocol specified procedures ... 88

4.3 Demographic characteristics ... 90
4.3.1 Total vaccinated cohort ... 90
4.3.2 Subjects included in the ATP cohort for efficacy analysis ... 90
4.3.3 Subjects included in the ATP cohort for immunogenicity analysis ... 91

5 Analysis of efficacy in subjects planned to receive two doses of HRV vaccine or placebo ... 92

5.1 Data sets analyzed ... 92

5.2 ATP analysis ... 92
5.2.1 Characterization of GE episodes reported during the first efficacy follow-up period . 92
5.2.2 Vaccine efficacy against RV GE during the first efficacy follow-up period ... 94
5.2.3 Vaccine efficacy against hospitalization due to RV GE during the first efficacy follow-up period ... 98
5.2.4 Total vaccinated cohort for efficacy analysis ... 99

5.2.4.1 Vaccine efficacy against RV GE occurring from Dose 1 onwards 99

6 Analysis of safety in subjects planned to receive two doses of HRV vaccine or placebo 101

6.1 Data sets analyzed 101

6.2 Total vaccinated cohort for safety analysis 102
6.2.1 Overall incidence of symptoms 102
6.2.2 Solicited signs and symptoms 103
6.2.3 Unsolicited symptoms 111
6.2.4 Concomitant medications 115
6.2.5 Reactogenicity analysis by country 117
6.2.6 Serious adverse events 117
6.2.6.1 SAEs assessed as possibly related to the concomitantly administered routine vaccination 118
6.2.6.2 SAEs with fatal outcome 118
6.2.6.3 IS 119
6.2.6.4 SAEs ongoing at the data lock point for analysis 121

6.3 ATP cohort for safety analysis 121

7 Analysis of immunogenicity in subjects planned to receive two doses of HRV vaccine or placebo 121

7.1 Data sets analyzed 121

7.2 ATP cohort for immunogenicity analysis 121
7.2.1 Immunogenicity of the HRV vaccine 121
7.2.2 Immunogenicity of the HRV vaccine in the stool analysis subset 123
7.2.3 Impact of feeding on immunogenicity of HRV vaccine 129
7.2.4 Immunogenicity analysis by country 129
7.2.5 Immunogenicity of routine vaccinations (DTPw-HB+Hib and OPV) 129

7.3 Total vaccinated cohort for immunogenicity analysis 137

8 Exploratory evaluation of three doses of HRV vaccine or placebo 137

8.1 Study population receiving three doses of HRV vaccine or placebo 137
8.1.1 Study dates 137

8.2 Subject eligibility and attrition from study 138
8.2.1 Number and distribution of subjects 138
8.2.2 Study completion and drop out 138
8.2.3 Eligibility for analysis 138
8.2.4 Compliance with protocol specified procedures 138

8.3 Demographic characteristics of the total vaccinated cohort 139

8.4 Exploratory analysis of efficacy 140
8.4.1 Data sets analyzed 140
8.4.2 Total vaccinated cohort for efficacy analysis 140
8.4.2.1 Characterization of GE episodes reported during the first efficacy follow-up period. 140

8.5 Analysis of safety 141
8.5.1 Data sets analyzed 141
8.5.2 Total vaccinated cohort for safety analysis 142
8.5.2.1 Overall incidence of symptoms 142
8.5.2.2 Solicited signs and symptoms 143
8.5.2.3 Unsolicited symptoms 150

8.5.2.4 Concomitant medications 152
8.5.3 Serious adverse events 154

8.6 Analysis of immunogenicity 155
8.6.1 Data sets analyzed 155
8.6.2 Total vaccinated cohort for immunogenicity analysis 155
8.6.2.1 Immunogenicity of GSK Biologicals' HRV vaccine 155
8.6.2.2 Immunogenicity of routine vaccinations (DTPw-HB+Hib and OPV) 158

9 Discussion 164

10 Overall Conclusions 168

11 References 171

CONTENTS: REPORT TABLES

TABLE 1: THE GSK ASSIGNED CENTRE NUMBERS, INVESTIGATIONAL SITES AND INVESTIGATORS.. 36
TABLE 2: ETHICS COMMITTEES FOR EACH CENTRE 37
TABLE 3: OUTLINE OF STUDY PROCEDURES 48
TABLE 4: THE 20-POINT SCORING SYSTEM USED TO ASSESS THE SEVERITY OF EACH DIARRHEA EPISODE 52
TABLE 5: INTENSITY SCALES FOR SOLICITED SYMPTOMS 54
TABLE 6: INTERVALS BETWEEN STUDY VISITS* FOR SUBJECTS PLANNED TO RECEIVE TWO DOSES OF HRV VACCINE OR PLACEBO 58
TABLE 7: INTERVALS BETWEEN STUDY VISITS* FOR SUBJECTS RECEIVING THREE DOSES OF HRV VACCINE OR PLACEBO 59
TABLE 8: SEROLOGICAL ASSAYS FOR ANTIBODIES TO CONCOMITANTLY ADMINISTERED ROUTINE VACCINATIONS 61
TABLE 9: POWER TO GET AN EXACT 95% CI FOR THE VACCINE EFFICACY FOR A VACCINE GROUP ABOVE A SPECIFIC CUT-OFF (N = 460 SUBJECTS BY GROUP, POWER BASED ON 1.000 SIMULATIONS USING PROC STATXACT) (REFER TO APPENDIX B FOR MATHEMATICAL DETAILS) 66
TABLE 10: THE NUMBER OF SUBJECTS ENROLLED AT EACH STUDY CENTRE BY GROUP (TOTAL VACCINATED COHORT) 84
TABLE 11: COUNTS OF SUBJECTS ENROLLED, COMPLETED, DROPPED OUT AND REASON FOR DROP OUT UNTIL THE END OF THE FIRST EFFICACY FOLLOW-UP PERIOD (TOTAL VACCINATED COHORT). 84
TABLE 12: NUMBER OF SUBJECTS ENROLLED INTO THE STUDY AS WELL AS THE NUMBER OF SUBJECTS EXCLUDED FROM ATP ANALYSES WITH REASONS FOR EXCLUSION 86
TABLE 13: SUMMARY OF DEMOGRAPHIC CHARACTERISTICS (ATP COHORT FOR EFFICACY ANALYSIS) 91
TABLE 14: NUMBER OF GE EPISODES AND RV GE EPISODES REPORTED DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY SEVERITY (ATP COHORT FOR EFFICACY ANALYSIS) 93
TABLE 15: PERCENTAGE OF SUBJECTS WITH RV GE EPISODES REPORTED DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY RV G TYPE (ATP COHORT FOR EFFICACY ANALYSIS) 94
TABLE 16: PERCENTAGE OF SUBJECTS REPORTING ANY RV GE AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (ATP COHORT FOR EFFICACY ANALYSIS) 96

TABLE 17: PERCENTAGE OF SUBJECTS REPORTING SEVERE RV GE AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (ATP COHORT FOR EFFICACY ANALYSIS) . 96
TABLE 18: PERCENTAGE OF SUBJECTS HOSPITALIZED DUE TO RV GE AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (ATP COHORT FOR EFFICACY ANALYSIS) . 99
TABLE 19: NUMBER AND PERCENTAGE OF SUBJECTS WHO RECEIVED VACCINE DOSE(S) (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 102
TABLE 20: PERCENTAGE OF DOSES AND OF SUBJECTS REPORTING SYMPTOMS (SOLICITED OR UNSOLICITED) DURING THE 15-DAY SOLICITED FOLLOW-UP PERIOD (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 103
TABLE 21: PERCENTAGE OF SUBJECTS WITH EACH SOLICITED SYMPTOM INCLUDING THOSE GRADED "2 OR 3", GRADED "3" IN INTENSITY AND THOSE CONSIDERED TO BE RELATED TO VACCINATION, DURING THE 15-DAY FOLLOW-UP PERIOD **AFTER DOSE 1** OF HRV VACCINE OR PLACEBO (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 105
TABLE 22: PERCENTAGE OF SUBJECTS WITH EACH SOLICITED SYMPTOM INCLUDING THOSE GRADED "2 OR 3", GRADED "3" IN INTENSITY AND THOSE CONSIDERED TO BE RELATED TO VACCINATION, DURING THE 15-DAY FOLLOW-UP PERIOD **AFTER DOSE 2** OF HRV VACCINE OR PLACEBO (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 107
TABLE 23: STATISTICAL COMPARISONS BETWEEN GROUPS FOR PERCENTAGE OF SUBJECTS REPORTING EACH SOLICITED SYMPTOM AFTER ANY DOSE OF HRV VACCINE OR PLACEBO (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 110
TABLE 24: THE PERCENTAGE OF SUBJECTS WITH UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS ASSESSED AS **RELATED** TO VACCINATION, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 111
TABLE 25: THE PERCENTAGE OF SUBJECTS WITH **GRADE "3"** UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 113
TABLE 26: PERCENTAGE OF DOSES WITH AT LEAST ONE CONCOMITANT MEDICATION ADMINISTERED FROM DAY 0 TO DAY 14 AFTER VACCINATION, BY TYPE (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 116
TABLE 27: ANTI-ROTAVIRUS IGA ANTIBODY GMCS AND SEROPOSITIVITY RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 122
TABLE 28: ANTI-ROTAVIRUS IGA ANTIBODY SEROCONVERSION RATES ON COMBINED DOSES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 123
TABLE 29: ANTI-ROTAVIRUS IGA ANTIBODY GMCS CALCULATED ON SUBJECTS SEROPOSITIVE FOR ANTI-ROTAVIRUS IGA ANTIBODIES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 123
TABLE 30: ANTI-ROTAVIRUS IGA ANTIBODY GMCS AND SEROPOSITIVITY RATE (STOOL ANALYSIS SUBSET, ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 124
TABLE 31: NUMBER OF SUBJECTS WITH VACCINE VIRUS IN STOOL SAMPLES COLLECTED AT PRE-DETERMINED TIMEPOINTS (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 126
TABLE 32: PERCENTAGE OF SUBJECTS WITH VACCINE VIRUS IN STOOL SAMPLES COLLECTED AT PRE-DETERMINED TIME POINTS, ON COMBINED TIME POINTS (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 127

TABLE 33: PERCENTAGE OF SUBJECTS WITH VACCINE TAKE AFTER EACH DOSE OF HRV VACCINE OR PLACEBO (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 127
TABLE 34: PERCENTAGE OF SUBJECTS WITH VACCINE TAKE AFTER COMBINED DOSES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 128
TABLE 35: DIFFERENCE IN PERCENTAGE OF SUBJECTS WITH VACCINE TAKE ON COMBINED DOSES 1 AND 2 AT TWO MONTHS AFTER DOSE 2 OF HRV VACCINE OR PLACEBO (AT VISIT 3) BETWEEN EACH HRV VACCINE AND PLACEBO GROUPS (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) ... 129
TABLE 36: ANTI-DIPHTHERIA ANTIBODY GMCS AND SEROPROTECTION RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 131
TABLE 37: ANTI-TETANUS ANTIBODY GMCS AND SEROPROTECTION RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 132
TABLE 38: ANTI-BPT ANTIBODY GMCS AND SEROPOSITIVITY RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 133
TABLE 39: ANTI-HBS ANTIBODY GMCS AND SEROPROTECTION RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 134
TABLE 40: ANTI-PRP ANTIBODY GMCS AND SEROPROTECTION RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 135
TABLE 41: ANTI-POLIOVIRUS TYPES 1, 2 AND 3 ANTIBODY GMTS AND SEROPROTECTION RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 136
TABLE 42: PERCENTAGE OF SUBJECTS REPORTING ANY RV GE FROM 2 WEEKS AFTER DOSE 3 OF HRV VACCINE OR PLACEBO UNTIL END OF THE FIRST EFFICACY FOLLOW-UP PERIOD (TOTAL VACCINATED COHORT FOR EFFICACY ANALYSIS) 141
TABLE 43: PERCENTAGE OF SUBJECTS REPORTING SEVERE RV GE FROM 2 WEEKS AFTER DOSE 3 OF HRV VACCINE OR PLACEBO UNTIL END OF THE FIRST EFFICACY FOLLOW-UP PERIOD (TOTAL VACCINATED COHORT FOR EFFICACY ANALYSIS) 141
TABLE 44: PERCENTAGE OF DOSES AND OF SUBJECTS REPORTING SYMPTOMS (SOLICITED OR UNSOLICITED) DURING THE 15-DAY SOLICITED FOLLOW-UP PERIOD (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 143
TABLE 45: PERCENTAGE OF SUBJECTS WITH EACH SOLICITED SYMPTOM INCLUDING THOSE GRADED "2 OR 3", THOSE GRADED "3" IN INTENSITY AND THOSE CONSIDERED TO BE RELATED TO VACCINATION, DURING THE 15-DAY FOLLOW-UP PERIOD AFTER **DOSE 1** OF HRV VACCINE OR PLACEBO (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 145
TABLE 46: PERCENTAGE OF SUBJECTS WITH EACH SOLICITED SYMPTOM INCLUDING THOSE GRADED "2 OR 3", THOSE GRADED "3" IN INTENSITY AND THOSE CONSIDERED TO BE RELATED TO VACCINATION, DURING THE 15-DAY FOLLOW-UP PERIOD AFTER **DOSE 2** OF HRV VACCINE OR PLACEBO (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 147
TABLE 47: PERCENTAGE OF SUBJECTS WITH EACH SOLICITED SYMPTOM INCLUDING THOSE GRADED "2 OR 3", THOSE GRADED "3" IN INTENSITY AND THOSE CONSIDERED TO BE RELATED TO VACCINATION, DURING THE 15-DAY FOLLOW-UP PERIOD AFTER **DOSE 3** OF HRV VACCINE OR PLACEBO (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 149

TABLE 48: THE PERCENTAGE OF SUBJECTS WITH UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS ASSESSED AS RELATED TO VACCINATION, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 151
TABLE 49: THE PERCENTAGE OF SUBJECTS WITH GRADE 3 UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 152
TABLE 50: PERCENTAGE OF DOSES WITH AT LEAST ONE CONCOMITANT MEDICATION ADMINISTERED FROM DAY 0 TO DAY 14 AFTER VACCINATION, BY TYPE (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 153
TABLE 51: ANTI-ROTAVIRUS IGA ANTIBODY GMCS AND SEROPOSITIVITY RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 156
TABLE 52: ANTI-ROTAVIRUS IGA ANTIBODY GMCS CALCULATED ON SUBJECTS SEROPOSITIVE FOR ANTI-ROTAVIRUS IGA ANTIBODIES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 157
TABLE 53: NUMBER OF SUBJECTS WITH VACCINE VIRUS IN STOOL SAMPLES COLLECTED AT PRE-DETERMINED TIMEPOINTS (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS)158
TABLE 54: ANTI-DIPHTHERIA ANTIBODY GMCS AND SEROPROTECTION RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 159
TABLE 55: ANTI-TETANUS ANTIBODY GMCS AND SEROPROTECTION RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 160
TABLE 56: ANTI-BPT ANTIBODY GMCS AND SEROPOSITIVITY RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 160
TABLE 57: ANTI-HBS ANTIBODY GMCS AND SEROPROTECTION RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 161
TABLE 58: ANTI-PRP ANTIBODY GMCS AND SEROPROTECTION RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 162
TABLE 59: ANTI-POLIOVIRUS TYPES 1, 2 AND 3 ANTIBODY GMTS AND SEROPROTECTION RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS)..... 163

CONTENTS: SUPPLEMENTS

Supplements 1–11 : Compliance and demography for subjects planned to receive two doses of HRV vaccine or placebo

Supplements 12–42 : Efficacy for subjects planned to receive two doses of HRV vaccine or placebo

Supplements 43–98 : Reactogenicity and safety for subjects planned to receive two doses of HRV vaccine or placebo

Supplements 99–167 : Immunogenicity for subjects planned to receive two doses of HRV vaccine or placebo

Supplements 168–188 : Exploratory evaluation of three doses of HRV vaccine

APPENDICES

APPENDIX A: CLINTRIAL ELIGIBILITY CODES
APPENDIX B: MATHEMATICAL DETAILS* ABOUT THE COMPUTATION OF THE 95%CI FOR VACCINE EFFICACY
APPENDIX C: LABORATORY ASSAYS

INDIVIDUAL DATA LISTING NOT PROVIDED SINCE SECOND YEAR EFFICACY FOLLOW-UP WAS ONGOING AT DATA LOCK POINT FOR THE ANALYSIS.

APPENDIX: SERIOUS ADVERSE EVENTS
- SERIOUS ADVERSE EVENTS TABLE
- CLINICAL NARRATIVES FOR THE SERIOUS ADVERSE EVENTS

APPENDICES: STUDY INFORMATION
- PROTOCOL
- REPRESENTATIVE SUBJECT INFORMATION SHEET
- RELEVANT PAGES OF CRF (UNIQUE PAGES ONLY)
- ONE PAGE CV (*curriculum vitae)* FOR PRINCIPAL INVESTIGATORS
- PUBLICATIONS REFERENCED IN THE REPORT

List of Abbreviations

AE	Adverse Event
ATP	According to Protocol
BCG	Bacillus Calmette-Guerin
BPT	*Bordetella pertussis*
$CCID_{50}$	median Cell Culture Infective Dose
CI	Confidence Interval
cm	Centimeter
eCRF	electronic Case Report Form
DTPw-HB+Hib	Diphtheria-tetanus-whole-cell pertussis-hepatitis B-*Haemophilus influenzae* type b vaccine
ELISA	Enzyme Linked Immunosorbent Assay
EL.U	ELISA units
EPI	Expanded Program on Immunization
ES	End of season
ffu	Foci forming units
GCP	Good Clinical Practice
GE	Gastroenteritis
GMC/T	Geometric Mean Concentration/Titer
GSK	GlaxoSmithKline
HBs	Hepatitis B surface antigen
HBV	Hepatitis B Vaccine
HRV	Human Rotavirus
HIV	Human Immunodeficiency Virus
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A
IS	Intussusception
IU	International Units
Kg	Kilogram
LCL	Lower Confidence Limit
LF	Limit Floculation
LL	Lower Limit
MedDRA	Medical Dictionary for Regulatory Activities
mcg	Microgram
mg	Milligram
mIU	Milli-International Units
ml	Milliliters
MOH	Ministry of Health
OPV	Oral Polio Vaccine
OU	Opacity Units
PID	Patient Identification Number
PRP	Polyribosyl Ribitol Phosphate
RDE	Remote Data Entry
RIBA	Recombinant ImmunoBlot Assay
RRV-TV	Rhesus-human Reassortant Rotavirus Vaccine TetraValent

RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
U	Units
UL	Upper Limit
WHO	World Health Organization
WRC	Worldwide Regulatory Compliance

Glossary of Terms

According to protocol cohort:	Includes all subjects enrolled in the study who met the criteria defined in the protocol for the considered analysis (efficacy, reactogenicity or immunogenicity).
Adverse event:	Any noxious, pathologic or unintended change in anatomical, physiologic and/or laboratory detected changes occurring in any phase of the clinical trial whether associated with vaccination or whether or not considered vaccine related.
Completed:	Subject who completed the final study visit foreseen in the protocol.
Diarrhea:	Three or more looser than normal stools within a day.
Diary card:	Individual card provided by the sponsor for each vaccinee after each vaccine dose designed to document the presence of solicited adverse events as well as any other sign/symptom the vaccinee might experience.
Drop out:	Subject who did not return for the final study visit foreseen in the protocol.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled:	Participated in the first visit of the study after written informed consent obtained from parents/guardians, determined to be eligible for inclusion in the study based upon strict adherence to inclusion/exclusion criteria.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in analysis.
Independent Data Monitoring Committee	The IDMC was responsible for safety monitoring during the [rotavirus] trials taking into account the

(IDMC)	potential benefits of the vaccine in different parts of the world.
First efficacy follow-up period:	**For subjects planned to receive two doses of HRV vaccine or placebo:** The first efficacy follow-up period started from two weeks after Dose 2 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age). **For subjects who received three doses of HRV vaccine or placebo:** The first efficacy follow-up period started from two weeks after Dose 3 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age).
Gastroenteritis:	Diarrhea.
Mixed rotavirus gastroenteritis:	Gastroenteritis associated with rotavirus and at least one other pathogen: An episode of rotavirus gastroenteritis for which at least one other pathogen was identified in stool sample(s) collected from the start of the gastroenteritis episode to the minimum of the following 2 timepoints either 7 days after the end of the gastroenteritis episode or the day before the next gastroenteritis episode, if subject had several episodes of gastroenteritis.

Pure rotavirus gastroenteritis:	Rotavirus gastroenteritis with no other identified concurrent pathogen infection.
Rotavirus gastroenteritis:	All rotavirus gastroenteritis (pure and mixed rotavirus gastroenteritis).
Rotavirus gastroenteritis caused by the circulating wild-type rotavirus strains:	**For the subset of subjects who received two doses of HRV or placebo:** • From Visits 1 to 3: all gastroenteritis episodes in which rotavirus other than vaccine strain was identified in a stool sample collected during the episode. • From Visit 3 onwards: all gastroenteritis episodes in which rotavirus was identified in a stool sample collected during the episode. **For the subset of subjects who received three doses of HRV or placebo:** • From Visits 1 to 4: all gastroenteritis episodes in which rotavirus other than vaccine strain was identified in a stool sample collected during the episode. • From Visit 4 onwards: all gastroenteritis episodes in which rotavirus was identified in a stool sample collected during the episode.
Rotavirus gastroenteritis for efficacy analysis:	**For the subset of subjects planned to receive two doses of HRV or placebo:** An episode of gastroenteritis (diarrhea) occurring at least two weeks after Dose 2 in which rotavirus other than vaccine strain was identified in a stool sample collected during the episode of gastroenteritis. **For the subset of subjects who received three doses of HRV or placebo:** An episode of gastroenteritis (diarrhea) occurring at least two weeks after Dose 3 in which rotavirus other than vaccine strain was identified in a stool sample collected during the episode of gastroenteritis. Stool samples collected from the start of the gastroenteritis episode to the minimum of the following 2 timepoints either 7 days after the end of the gastroenteritis episode or the day before the next

	gastroenteritis episode, if subject had several episodes of gastroenteritis were considered.
Separate episodes of gastroenteritis:	Two occurrences of gastrointestinal symptoms with 5 or more symptoms-free days between the episodes.
Second efficacy follow-up period:	Second efficacy follow-up took place after visit at the end of the first efficacy follow-up period until a maximum of two years of age. The second efficacy follow-up period ended in June 2003 after the end of the 2003 rotavirus season in Mexico (for subjects from Mexico) and in October 2003 (for subjects from Brazil and Venezuela).
Seroconversion:	Appearance of anti-rotavirus IgA antibody concentration ≥ 20 units (U)/milliliter (ml in subjects initially (i.e. prior to the first dose of HRV vaccine or placebo) negative for rotavirus.
Seronegative:	A subject whose antibody concentration was below the assay cut-off value.
Seropositive:	A subject whose antibody concentration was greater than or equal to the assay cut-off value.
Seroprotected:	A subject whose antibody concentration was greater than or equal to the seroprotective level.
Severe rotavirus gastroenteritis:	An episode of rotavirus gastroenteritis with score ≥ 11 on a 20 point scoring system.
Subject(s)/Vaccinee(s):	Terms used throughout the report to denote the enrolled/vaccinated individual(s).
Symptom sheets:	The specific pages in the individual case report forms onto which the investigator transcribed diary card documentation on solicited symptom(s) reported for the subject.
Total vaccinated cohort:	All subjects with at least one study vaccine administration documented.

Vaccine take: The appearance of serum IgA to rotavirus in post-immunization sera at a concentration ≥ 20 U/ml and/or vaccine virus shedding in any stool sample collected from Visit 1 to Visit 3.

In Study 006, vaccine take was calculated only for the stool analysis subset (subjects who provided blood and stool samples).

Vomiting: One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

1 Introduction/Rationale

An attenuated human rotavirus (HRV) vaccine candidate was developed from the 89-12 HRV strain belonging to the serotype G1P1A and genotype [P8]. Initial development of the 89-12 vaccine at passage 33 has demonstrated its safety, immunogenicity and efficacy in infants ([1], [2]). GlaxoSmithKline (GSK) Biologicals has implemented several process changes to the 89-12 vaccine candidate at passage 33 to develop a lyophilized HRV vaccine containing a cloned 89-12 HRV strain at passage 43, referred to as RIX4414.

Study rota-006 was a randomized, placebo-controlled, double-blind, dose-range study conducted in Brazil, Mexico and Venezuela to assess the efficacy, reactogenicity, safety and immunogenicity of two doses of GSK Biologicals' HRV vaccine at different viral concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ foci forming units (ffu)) in healthy infants (approximately 2 months of age at first dose of HRV vaccine or placebo) following a 0, 2 month schedule. This study also assessed the immunogenicity of routine vaccinations: diphtheria-tetanus-whole-cell pertussis-hepatitis B-*Haemophilus influenzae* type b vaccine (DTPw-HB+Hib vaccine)] given concurrently with HRV vaccine or placebo and Oral Polio Vaccine (OPV) given separately outside a 2-week interval from HRV vaccine/placebo. All subjects were followed for efficacy until approximately one year of age. The efficacy, reactogenicity, safety and immunogenicity results obtained until the end of the first efficacy follow-up period after vaccination are presented in this study report.

Administration of a third dose of the HRV vaccine or its placebo at approximately 6 months of age was explored in a subset of subjects and results of this evaluation are also presented in this study report.

A subset of subjects participated in the second efficacy follow-up period (until maximum age 24 months). A separate annex report will present efficacy and safety data during the second efficacy follow-up period from all subjects (from Brazil, Mexico and Venezuela) who were followed until maximum age 24 months.

A subset of subjects from Mexico participated in study rota-008, an annex protocol titled "To assess the impact of breast milk lactadherin, breast milk rotavirus Immunoglobulin A (IgA) antibodies and maternal IgG antibodies on the immunogenicity of GSK Biologicals' HRV vaccine". The analyses for transplacental anti-rotavirus IgG antibodies and transplacental anti-rotavirus neutralizing antibodies in study rota-008 are available and are presented in the report "The Interference of Transplacental Antibodies on Response to GSK Biologicals' Human Rotavirus Vaccine: Rota-004, Rota-008 and Rota-014". A separate report will present all data obtained in study rota-008.
A subset of subjects from Venezuela participated in a site-specific evaluation of fecal RV IgA immune response and the role of IgA antibodies as marker of protection against RV disease. A separate report will present all data from this evaluation.

A separate report will present all data on characterisation of the immune response of the HRV vaccine (maternal antibodies and neutralizing antibodies) from subsets of subjects enrolled in study rota-006.

2 Study Objectives

Note: Although all study objectives are listed, only analyses of data obtained until the end of the first efficacy follow-up period are presented in this study report.

2.1 Primary objective

For the subset of subjects planned to receive two doses of HRV or placebo:

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine, to demonstrate the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations in preventing any rotavirus (RV) gastroenteritis (GE) during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period.

Refer to the glossary of terms for definition of terms used.

See Section 3.15.1 for delineation of the primary endpoint.

2.2 Secondary objectives

Efficacy

First efficacy follow-up period

For the subset of subjects planned to receive two doses of HRV or placebo:

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine, to assess if two doses of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations can:
  - Prevent severe RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
  - Prevent RV GE due to virus types heterologous to vaccine strain from two weeks after Dose 2 until the end of the first efficacy follow-up period.
  - Prevent any and severe pure RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
  - Prevent mixed RV GE (GE associated with RV and at least one other pathogen) during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
  - Prevent any hospitalization for RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.

For the subset of subjects who received three doses of HRV or placebo:

- To explore the rates of any and severe RV GE during the period starting from 2 weeks after Dose 3 until the end of the first efficacy follow-up period.

Second efficacy follow-up period (for a subset of approximately 1000 subjects)

- To evaluate the efficacy of the HRV vaccine during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period, and during the period starting from 2 weeks after the last HRV/placebo dose until the end of the second efficacy follow-up period.

Safety/Reactogenicity

- To assess the safety and reactogenicity of two doses of GSK Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo.
- To assess the safety and reactogenicity of the third dose of GSK Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo in a subset of subjects.

Immunogenicity

For the subset of subjects planned to receive two doses of HRV or placebo:

- To assess vaccine take, in subjects previously uninfected with RV before vaccination, two months after each study vaccine dose in the stool analysis subset.
- To assess persistence of serum IgA to RV at the end of the first efficacy follow-up period.
- To explore in a subset of subjects the effect of GSK Biologicals' HRV vaccine on the immune response to concurrently administered routine vaccinations.
- To explore the effect of unrestricted feeding on the immunogenicity of the vaccine.
- To assess viral shedding in the vaccine groups in the stool analysis subset.

For the subset of subjects who received three doses of HRV or placebo:

- To assess serum IgA to RV, two months after Dose 2 and Dose 3 of study vaccine or placebo.
- To assess viral shedding in the vaccine groups after the third HRV vaccine dose.
- To explore the effect of GSK Biologicals' HRV vaccine on the immune response to concurrently administered routine vaccinations two months after the third dose of routine vaccines.

See Section 3.15.2 for delineation of secondary endpoints.

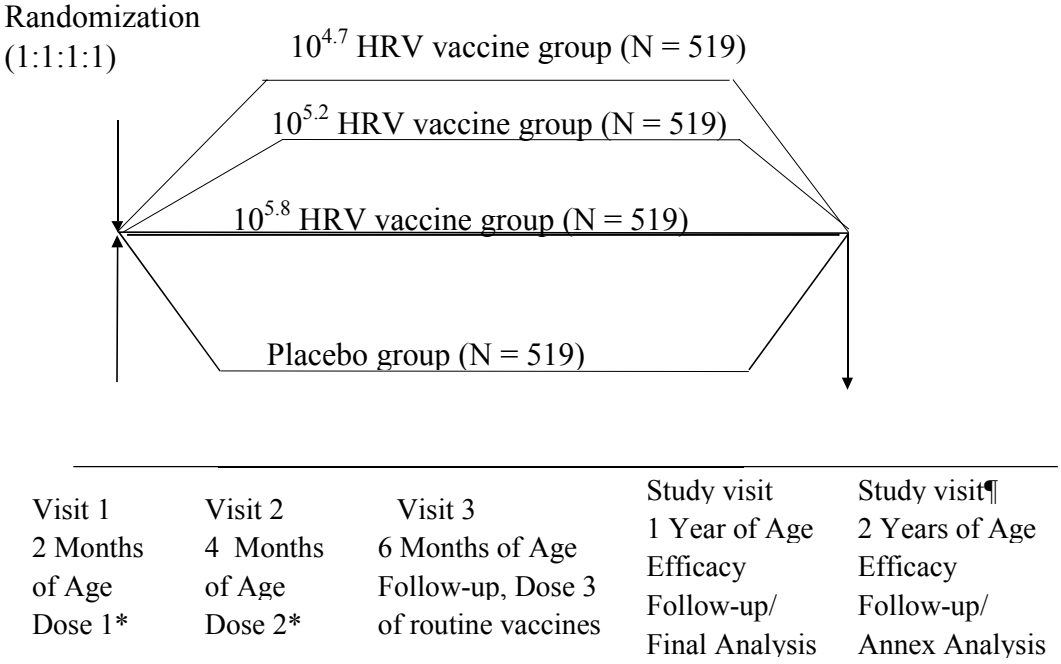
3 Methodology

Appendices: Study Information contains the study protocol, a representative subject information sheet and unique pages of the individual electronic Case Report Forms (eCRFs) utilized in the study.

3.1 Study design

Experimental design

For the subset of subjects planned to receive two doses of HRV vaccine or placebo:

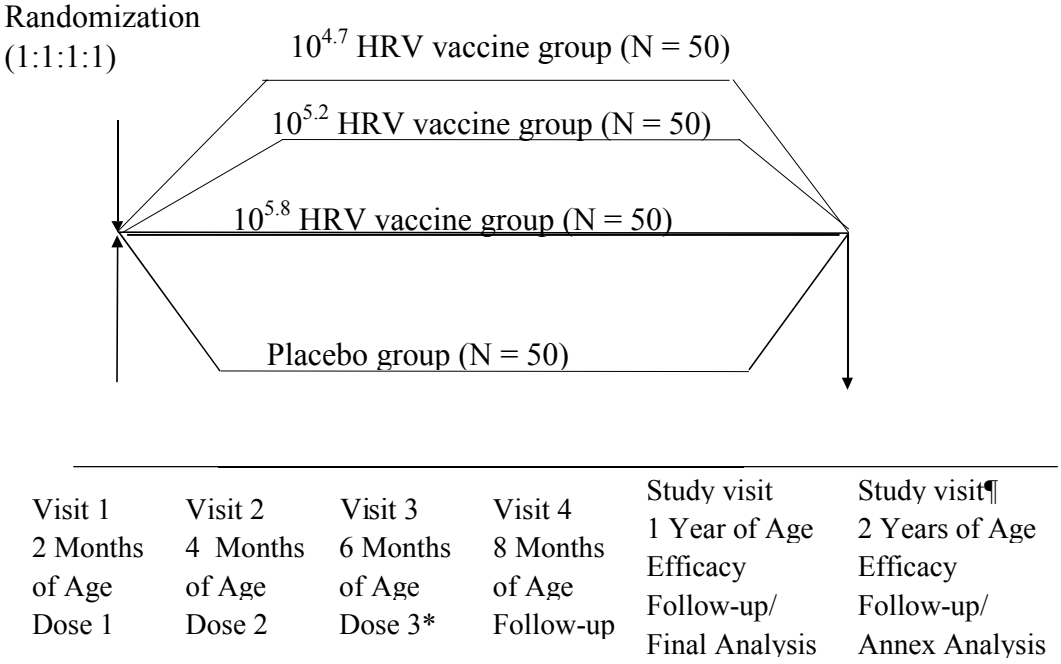


N = planned number of subjects

* HRV vaccine or placebo and concomitant routine vaccines

¶In a subset of subjects

For the subset of subjects who received three doses of HRV or placebo:



N = planned number of subjects

*HRV vaccine or placebo and concomitant routine vaccines

¶In a subset of subjects

This was a double-blind, randomized, placebo-controlled study consisting of four parallel groups with balanced allocation (1:1:1:1). The parents or guardians of the subjects and the study personnel (the investigator, study nurses and other personnel from the investigator's team who were involved in the study) were unaware of the administered treatment (HRV vaccine or placebo) during the entire study period until study end.

Data collection was performed using remote data entry (RDE).

Administration of Hepatitis B vaccine (HBV), Bacillus Calmette-Guerin (BCG) vaccine and OPV at birth was allowed according to local Expanded Program of Immunization (EPI) and was to be recorded in the eCRF.

There were no restrictions on feeding the infants before or after study vaccine or placebo administration.

Information on feeding on the day of each study vaccine administration was recorded for all subjects. The parents/guardians were questioned whether the child was fed with breast milk or infant formula and whether the child was fed within 60 minutes before study vaccination and/or within 30 minutes after study vaccination.

Subjects receiving two doses of HRV vaccine or placebo were to receive routine vaccinations (DTPw-HB+Hib vaccine) concomitantly with the study vaccines at 2 and 4 months of age; thereafter, DTPw-HB+Hib vaccine was to be given at 6 months of age.

Subjects receiving three doses of HRV vaccine or placebo were to receive routine vaccinations (DTPw-HB+Hib vaccine) concomitantly with each dose of HRV vaccine or placebo.

OPV was to be given at the discretion of the investigator, but was not to be administered during the period starting 2 weeks before each dose of HRV vaccine or placebo and ending 2 weeks thereafter.

Administration of all routine vaccinations, including OPV, was to be documented in the eCRF.

All subjects were followed for efficacy until approximately one year of age.

A subset of approximately 1000 subjects participated in the second efficacy follow-up period (until maximum age 24 months). The second efficacy follow-up period in Mexico ended in June 2003 (after the end of the 2003 RV season). The second efficacy follow-up period in Brazil and Venezuela ended in October 2003.

For the subjects who participated only in the first efficacy follow-up period (until approximately one year of age), the intended duration of the study, per subject, was approximately 10 months.

For the subset of subjects who participated in a second efficacy follow-up period, the intended duration of the study, per subject, was 22 months at most.

An Independent Data Monitoring Committee (IDMC) was monitoring the safety aspects of the HRV vaccine clinical development: i.e. each Serious Adverse Event (SAE) or Intussusception (IS) case was reviewed by this committee.

3.2 Investigators and trial centres

Appendices: Study Information contains the *curriculum vitae* of the principal investigators.

This multicentre study was conducted independently in Brazil, Mexico and Venezuela.

Table 1 provides the GSK assigned centre numbers, investigational sites and investigators in each country.

Table 1: The GSK assigned centre numbers, investigational sites and investigators

GSK assigned centre number	Investigational site	Principal Investigators	Co-investigators
[redacted]	[redacted] / Brasil	Dr. [redacted] M.D., Ph.D.	Dr. [redacted] B.Sc, Ph.D. Dr. [redacted] M.D. Dr. [redacted] M.D. Dr. [redacted] M.D. Dr. [redacted] M.D.
[redacted]	[redacted] México,	Dr. [redacted] M.D.	Dra. [redacted] M.D., M.S.
[redacted]	[redacted] Venezuela	Dra. [redacted] M.D. Dra. [redacted] Ph.D as the Principal Study Co-ordinator	Dra. [redacted] M.D. Dra. [redacted] M.D.

3.3 Ethics

The study was conducted according to Good Clinical Practices (GCP) and in accordance with the Declaration of Helsinki as amended in Somerset West, Republic of South Africa in October 1996.

Written informed consent was obtained from each subject's parent or guardian prior to entry into the study.

Standardized eCRFs were provided for each subject's data to be recorded.

The study protocol dated October 20, 2000 and the statement of informed consent were approved by the Ethics Committees mentioned in Table 2 as well as the Ministry of Health (MOH) in each country prior to study initiation.

Table 2: Ethics Committees for each centre

Study centre	Ethics Committees
Brazil	[redacted] / Brasil
Mexico	[redacted] México,
Venezuela	[redacted] -, Venezuela

All subsequent amendments were also submitted to the above-mentioned Ethics Committees and the changes to the protocol were implemented after approvals from the respective Ethics Committees' were obtained.

All submitted amendments were approved, except for Amendment 3 in Venezuela (see Section 3.3.1 for information on Amendment 3). The amendment was rejected since the Ethics Committee in Venezuela felt that administration of an additional dose (third dose of HRV vaccine or placebo) would affect the reputation of the principal investigator since over 90% of the subjects would be part of the two-dose subset and only a small number of subjects (approximately 45 subjects) would be part of the three-dose subset.

3.3.1 Protocol amendments/modifications

Amendment 1: The first amendment dated February 12, 2001 was done to correct the actual release titer of one of the clinical lots used in this study, to direct parents/guardians to contact study personnel for every case of GE, to define the subsets for serum and stool analyses, delete GE stool testing for cryptosporidia and to clarify the use of several commercial lots for the routine vaccines.

Modification 1: The first modification dated May 14, 2001 was done to implement changes in study personnel in Brazil and Venezuela.

Site-specific amendment for Venezuela: The site-specific amendment dated October 10, 2001 was done to evaluate fecal RV IgA immune response and the role of IgA antibodies as marker of protection against RV disease in a subset of 200 infants from Venezuela. Analysis and reporting of the data from tests performed on the additional stool samples from the subset of 200 subjects in Venezuela is the responsibility of Dra. [redacted] the principal investigator in Venezuela. A separate report will present data obtained during the site-specific evaluation.

Amendment 2: The second amendment dated December 11, 2001 was done to allow termination of enrolment in Mexico by end December 2001 to avoid vaccinating subjects during the RV season and to change the addresses of the GSK offices in Brazil and Mexico.

Amendment 3: The third amendment dated May 3, 2002 was done to allow administration of a third dose of the HRV vaccine or placebo to a subset of 200 infants in order to explore a three-dose schedule and to decrease the sample size from 2640 subjects to 2276 subjects because of difficulty in enrolling eligible subjects for participation in the study.

Amendment 4: The fourth amendment dated July 11, 2002 was done to allow an interim analysis in order to provide early information on the efficacy of the HRV vaccine against any and severe RV GE in Latin America.

Amendment 5: The fifth amendment dated September 20, 2002 was done to add a second efficacy follow-up period (until maximum age 24 months) for the subjects who had not completed the study as of October 31, 2002.

Amendment 6: The sixth amendment dated March 26, 2003 was done to implement the use of a ‘Standard Verbal Autopsy Questionnaire’ as per the IDMC's recommendation, to remove co-pathogen testing for all subjects during the second efficacy follow-up period, to allow termination of follow-up of Mexican subjects after the end of the 2003 RV season in Mexico and to allow an interim efficacy analysis at the end of the second efficacy follow-up period in Mexico.

Amendment 7: The seventh amendment dated August 21, 2003 was done to allow study end in October 2003 by terminating the second efficacy follow-up of subjects in Brazil and Venezuela.

Annex Study 444563(rota)008 in Mexico: Additionally, an annex protocol dated November 29, 2000 was implemented in Mexico (study rota-008) to characterize the immune response of the HRV vaccine in subjects participating in study rota-006 in Mexico. The aim of the study was to assess the impact of breast-milk lactadherin, breast-milk anti-rotavirus IgA antibodies and maternal IgG antibodies on immunogenicity of the HRV vaccine. Mothers of approximately 200 subjects, who were enrolled in study rota-006 and were part of the subset providing blood samples at post-vaccination timepoints, participated in study rota-008. The analyses for transplacental anti-rotavirus IgG antibodies and transplacental anti-rotavirus neutralizing antibodies in study rota-008 are available and are presented in the report "The Interference of Transplacental Antibodies on Response to GSK Biologicals' Human Rotavirus Vaccine: Rota-004, Rota-008 and Rota-014". A separate report will present all data on characterization of the immune response of the HRV vaccine.

3.4 Selection of study population

The study population consisted of healthy male and female infants enrolled after checking the eligibility criteria at study entry.

3.4.1 Inclusion criteria

The following criteria were checked at the time of study entry.

- A male or female between, and including, 6 and 12 weeks (42–90 days) of age at the time of the first vaccination.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Written informed consent obtained from the parents or guardians of the subject.
- Born after a normal gestation period (between 36 and 42 weeks) or with a birth weight > 2000 g.

3.4.2 Exclusion criteria

The following criteria were checked at the time of study entry. If any applied at the time of study entry, the infant was not included in the study:

- Use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the study vaccine or placebo or planned use during the study period.

- Planned administration of a vaccine (including routine paediatric vaccines) not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine and ending 14 days after.
- Planned administration of OPV during the period starting from 2 weeks before each dose of study vaccine and ending 2 weeks after.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth. (Topical steroids were allowed.)
- History of previous diphtheria, tetanus, pertussis, Hib disease and/or hepatitis B.
- Previous vaccination against diphtheria, tetanus, pertussis and/or Hib.
- Use of antibiotics within 7 days preceding Dose 1 of study vaccine (warranted deferral of vaccination pending recovery of the subject).
- Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malfunction of the gastrointestinal tract or other serious medical condition as determined by the investigator.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
- History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.
- Acute disease at time of enrolment. (Acute disease was defined as the presence of moderate or severe illness with fever i.e. temperature ≥ 37.5°C as measured by an axillary thermometer or ≥ 38.0°C as measured by a rectal thermometer). A temperature greater than or equal to these cut-offs warranted deferral of vaccination pending recovery of the subject.
- GE within 7 days preceding the study vaccine administration (warranted deferral of the vaccination).
- Household contact with an immunosuppressed individual or pregnant woman.
- Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
- Previous confirmed occurrence of RV GE.

3.4.3 Elimination criteria during the study up to Visit 3 (up to Visit 4 for the subset of subjects receiving three doses of study vaccine or placebo)

The following criteria were checked at Visits 2 and 3. These elimination criteria were also checked on the day of Dose 3 of the study vaccine or placebo in a subset of subjects (at Visit 4). If any became applicable during the study, the subject was not required to discontinue the study but could be eliminated from the according-to-protocol (ATP) cohort analyses.

- Use of any investigational or non-registered drug or vaccine other than the study vaccine during the study period.

- Use of antibiotics during the period starting from 7 days before Dose 1 and 2 of study vaccine and ending 7 days after.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
- Administration of a vaccine (including routine paediatric vaccines) not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.
- Administration of OPV during the period starting from 2 weeks before each dose of study vaccine and ending 2 weeks after.
- Administration of immunoglobulins and/or any blood products during the study period.
- Confirmed immunosuppressive or immunodeficient condition, including HIV.

3.4.4 Elimination criteria during the study from Visit 3 (from Visit 4 for the subset of subjects receiving three doses of study vaccine or placebo) until study end

If any became applicable during the study, the subject was not required to discontinue the study but could be eliminated from the ATP cohort analyses.

- Use of any investigational or non-registered drug or vaccine other than the study vaccine during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids were allowed.)
- Administration of immunoglobulins and/or any blood products during the study period.
- Confirmed immunosuppressive or immunodeficient condition, including HIV.

3.4.5 Contraindications to vaccination

GSK Biologicals' HRV vaccine or placebo

The following adverse events (AEs) constituted absolute contraindications to further administration of GSK Biologicals' HRV vaccine or placebo; if any of these AEs occurred during the study, the subject did not receive additional doses of HRV vaccine or placebo but could continue other study procedures at the discretion of the investigator. The subject was followed until resolution of the event, as with any AE:

- Hypersensitivity reaction due to the vaccine.
- Intussusception (IS).

The following AEs constituted contraindications to administration of HRV vaccine or placebo at that point in time; if any one of these AEs occurred at the time scheduled for vaccination, the subject could be vaccinated at a later date, within the time window specified in the protocol, or withdrawn at the discretion of the investigator. The subject was followed until resolution of the event, as with any AE:

- Axillary/rectal temperature ≥ 37.5/38.0°C.
- GE within 7 days preceding the study vaccine administration.

Routine DTPw-HB+Hib vaccine

The following AEs constituted absolute contraindications or precautions to further administration of routine DTPw-HB+Hib vaccine; if any of these AEs occurred during the study, the subject was withdrawn and followed until resolution of the event, as with any AE:

- Known hypersensitivity to any component of the vaccine or subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B or Hib vaccines.
- Encephalopathy (not due to another identifiable cause). This was defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, and/or generalized or focal seizures that persisted more than a few hours, with failure to recover within 24 hours. Even though causation by DTP-containing vaccine has not been established, no subsequent doses of pertussis vaccine were to be given.

If the following AEs occurred in temporal relation to DTPw-HB+Hib vaccine administration, the decision to administer additional doses of DTPw-HB+Hib vaccine was to be carefully considered:

- Fever ≥ 40.5°C/≥ 40.0°C (rectal/axillary temperature) within 48 hours of vaccination not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting >3 hours, occurring within 48 hours of vaccination.
- Seizures with or without fever occurring within 3 days of vaccination.

3.5 Study vaccines and administration

The study vaccines used were developed and manufactured by GSK Biologicals, Belgium.

The Quality Control Standards and Requirements for each vaccine are described in separate release protocols and the required approvals were obtained. The vaccine release protocols are archived in the study file and are available upon request.

3.5.1 GSK Biologicals' HRV vaccine

One dose of lyophilized HRV vaccine contained the following components:

RIX4414 (derived from the 89-12 HRV strain)	$10^{4.7}$ ffu, $10^{5.2}$ ffu or $10^{5.8}$ ffu
Sucrose	9 milligram (mg)
Dextran	18 mg
Sorbitol	13.5 mg
Amino acids	9 mg

Lot number DRVC005A46 was used for HRV vaccine $10^{4.7}$ ffu.
Lot number DRVC010A48 was used for HRV vaccine $10^{5.2}$ ffu.
Lot number DRVC004A46 was used for HRV vaccine $10^{5.8}$ ffu.

3.5.2 GSK Biologicals' placebo for HRV vaccine

One dose of lyophilized placebo contained the following components:

Sucrose	9 mg
Dextran	18 mg
Sorbitol	13.5 mg
Amino acids	9 mg

Lot numbers DRVC014A48PL and DRVC006A46PL were used.

3.5.3 GSK Biologicals' calcium carbonate buffer used as diluent

Each pre-filled syringe of 1.3 ml in volume contained the following components per 1.0 ml:

Calcium carbonate	60 mg
Xanthane 0.25 % in water for injection	1.0 ml

Lot numbers 00J03/1010, 00I19/1006, 00J03/1010, 00J04/1011 and 01C09/1013 were used for the diluent.

3.5.4 Dosage and administration

The HRV vaccine or placebo was prepared for administration by injecting the entire content of one pre-filled syringe containing the calcium carbonate buffer into the vial of the lyophilized product (vaccine or placebo). The vial was shaken well to

resuspend the vaccine/placebo. The entire volume of the resuspended product was withdrawn into the same syringe, the needle discarded and the resuspended product administered promptly as a single oral dose (approximately 1.0 ml).

Subjects received two doses of the reconstituted HRV vaccine or its placebo orally at Visits 1 and 2. A subset of subjects received a third dose of the reconstituted HRV vaccine or its placebo orally at Visit 3.

The subjects were observed closely for at least 30 minutes, with appropriate medical treatment readily available, in case of a rare anaphylactic reaction following the administration of vaccine.

3.6 Routine vaccines and administration

Commercially available routine vaccines were assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

3.6.1 GSK Biologicals' DTPw-HB+Hib vaccine

The DTPw-HB+Hib vaccine was supplied as two individual components, liquid DTPw-HB vaccine and lyophilized Hib vaccine, in monodose vials.

One dose (0.5ml) of DTPw-HB vaccine contained the following components:

Active ingredients	
Bordetella pertussis, killed	not less than 4 International Units (IU) (Lower Confidence Limit (LCL): not less than 2 IU) [15 Opacity Units (OU)]
Diphtheria toxoid	LCL not less than 30 IU (7.5 Limit Floculation (Lf))
Tetanus toxoid	LCL not less than 60 IU (3.25 Lf)
Recombinant DNA Hepatitis B virus surface antigen	10 microgram (mcg)
Other ingredients	
2-phenoxyethanol	0.5 mg
Aluminium as aluminium phosphate and aluminium hydroxide	0.63 mg
Sodium chloride	4.5 mg
Thiomersal	25 mcg
Water for injection	ad 0.5 ml

One dose (0.5ml) of Hib vaccine contained the following components:

Active ingredients

Conjugate of 10 mcg *Haemophilus influenzae* type b capsular polysaccharide, polyribosyl ribitol phosphate (PRP), and tetanus toxoid

Excipient

Lactose	12.6 mg

Commercial lots of DTPw-HB and Hib vaccines were used.

3.6.2 GSK Biologicals' OPV (Polio Sabin) vaccine

OPV vaccine was supplied as a liquid preparation. One dose (0.5ml) of OPV vaccine contained the following components:

Poliovirus type 1 (LS-c, 2ab)	not less than 10^6 to $10^{6.5}$ $CCID_{50}$
Poliovirus type 2 (P712, Ch, 2ab)	not less than 10^5 to $10^{5.5}$ $CCID_{50}$
Poliovirus type 3 (Leon $12a_1b$)	not less than $10^{5.8}$ to 10^6 $CCID_{50}$
Magnesium chloride	20.33 mg
Neomycin	≤ 5 µg

$CCID_{50}$ = median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)

Commercial lots of OPV vaccine were used.

3.6.3 Dosage and administration

The DTPw-HB+Hib vaccine was to be prepared according to the manufacturer's recommendations and administered intramuscularly into the anterolateral thigh using a 23- or 25- gauge needle. Subjects were to receive one dose (0.5 ml) of DTPw-HB+Hib vaccine at Visits 1, 2 and 3.

The OPV vaccine was prepared according to the manufacturer's recommendations. Three doses of OPV were to be given at the discretion of the investigator, but were not to be administered during the period starting 2 weeks before each dose of study vaccine or placebo and ending 2 weeks after.

3.7 Treatment allocation and randomization

3.7.1 Randomization of supplies

A randomization list was generated at GSK Biologicals, Rixensart, Belgium using a standard SAS® (Statistical Analysis System) program to number vaccine doses.

A randomization blocking scheme (1:1:1:1 ratio) was used to ensure that balance between treatments was maintained: a unique randomization number identified the vials to be administered to the same subject. The vaccine doses were distributed to the study sites while respecting the randomization block size.

To allow GSK Biologicals' to take advantage of greater than anticipated rates of recruitment at individual centres in this multicentre study, and to reduce the overall study recruitment period, a 10% over-randomization of supplies was prepared. However, enrolment was terminated when the target sample size was reached.

3.7.2 Randomization of subjects

All study centres used a central randomization system using the Internet, except in case of unexpected technical problems, to randomly allocate eligible subjects to a study group. The randomization algorithm used a minimisation procedure stratified by centre ([3]). When central randomization was not possible due to unexpected technical problems, manual randomization took place (selecting the higher patient identification numbers (PIDs) available).

Each subject was given vaccine doses identified with the unique randomization (or vaccine) number assigned to him/her. The vaccine number was also used as PID for all data collected for the subject during the study.

3.7.3 Subset definition

Subsets to evaluate immunogenicity of two doses of HRV vaccine or placebo
A subset of approximately 800 subjects were planned to provide blood samples at Visits 2 and 3 and an additional amount of blood at study visit at the end of the first efficacy follow-up period. The first 200 enrolled subjects in each participating country constituted this subset. The remaining 200 subjects in this subset were included according to the order of enrolment irrespective of their country.

Stool analysis subset
A subset of approximately 400 subjects were planned to provide stool samples on the day of Dose 1 and Dose 2, and on Day 7±1 following each dose of HRV vaccine or placebo. The first 100 enrolled subjects in each participating country constituted this subset. The remaining 100 subjects in this subset were included according to the order of enrolment irrespective of their country. The approximately 400 subjects constituting the stool analysis subset were part of the subset providing blood samples at Visits 2 and 3. This subset was used to calculate vaccine take since serology and shedding data were both available only for this subset.

Subset receiving three doses of HRV vaccine or placebo
A subset of 200 subjects from Brazil and Venezuela was planned to receive a third dose of HRV vaccine or placebo at 6 months of age (at Visit 3). As the protocol was not approved in Venezuela, this subset only constituted the last 121 subjects enrolled in Brazil. This subset provided blood samples at Visit 3 (day of Dose 3 of HRV vaccine or placebo) and at Visit 4 (two months after Dose 3 of HRV vaccine or placebo). This subset also provided stool samples on the day of and on Day 7±1 after Dose 3 of HRV vaccine or placebo.

Subset followed for efficacy until maximum 24 months of age
All subjects who had not completed the follow-up visit at one year of age as of October 31, 2002 were part of the subset (N = approximately 1000) to be followed for efficacy during the second efficacy follow-up period (until maximum age 24 months). This subset had an additional study visit at the end of the second efficacy follow-up period for GE follow-up. The second efficacy follow-up period in Mexico ended in June 2003 (after the end of the 2003 RV season). In Brazil and Venezuela, the second efficacy follow-up period ended in October 2003.

3.8 Blinding

This study was conducted in a double-blind manner. The parents or guardians of the subjects and the study personnel were unaware of the administered treatment (HRV vaccine or placebo) during the entire study period until study end.

Selected persons (not part of the investigative or sponsor clinical teams) using the central randomization system could perform unblinding. The code could be broken by the Clinical Safety Physician only in the case of medical events, which the investigator or physician in charge of the subject felt could not be treated without knowing the identity of the study vaccine.

The IDMC had access to the individual treatment codes and could at its discretion identify the product administered to any subject to evaluate whether enrolment in the study had to be halted.

In the event that the code was broken, the reason was recorded in the eCRF and in the subject's medical record.

During analysis at the end of the first efficacy follow-up period, only the statistician and database administrator had access to the individual treatment code for all subjects. In addition, access to the individual treatment code for some subjects was made available within GSK personnel, after the database was frozen for the analysis at the end of the first efficacy follow-up period, for the purpose of interim analyses of the research protocols related to study rota-006.

Moreover, access to the individual treatment code was made available for all SAEs after the database was frozen for the analysis at the end of the first efficacy follow-up period.

In this study report, only summary results without the individual subjects' treatment code (except for SAEs) are provided and individual subjects' numbers are not specified.

3.9 Study procedures

The study procedures carried out at each visit are given in Table 3.

Table 3: Outline of study procedures

Age	**2 months**	**4 months**	**6 months**	**8 months**	**1 year**	**18-24 Mo**
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4 Dose 3 subset only***	**End of 1st Efficacy Period**	**End of 2nd Efficacy Period**
Sampling timepoint	Pre	Post vacc 1	Post vacc 2 M4	Post vacc 3 M6	Post vacc 2 M10	
Informed consent	•					
Medical history	•					
Check of inclusion criteria	•					
Check of exclusion criteria	•					
Check of elimination criteria		•	•	•	•	•
Check of contraindications	•	•	•			
Physical examination	•	•	•	•	•	•
Pre-vaccination body temperature	•	•	•			
Measure/record height and weight	•	•	•	•	•	•
Blood sampling	• (1 ml)	• (1 ml#)	• (3 ml#) • (1 ml*)	• (3 ml*)	• (3 ml#, 1 ml)	
Randomization	•					

Source: Protocol and sample eCRF in *Appendices: Study Information*
Notes: #Subset *Subset receiving three doses of HRV vaccine/placebo
¶For subjects who participated only in the first efficacy follow-up period
§For subjects who participated in a second efficacy follow-up period

Table 3 (continued): Outline of study procedures

Age	2 months	4 months	6 months	8 months	1 year	18-24 Mo
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4***	**End of 1st Efficacy Period**	**End of 2nd Efficacy Period**
Sampling timepoint	Pre	Post vacc 1	Post vacc 2 M4	Post vacc 3 M6	Post vacc 2 M10	
Stool samples will be collected from a subset (N = 400) on the day of administration of Dose 1 and Dose 2 and on Day 7±1 following each study vaccine dose. Stool samples will be collected from a subset (N ~ 200) on the day of administration of Dose 3 and on Day 7±1 following Dose 3 of study vaccine	•	•	•*			
Study Vaccine	•	•	•*			
Routine Vaccination	•	•	•			
Daily post-vaccination recording of solicited symptoms (Days 0–14) by parents/guardians	•	•	•*			
Collection of stool samples if the child is suspected to have GE	•	•	•	•	•	•
Recording of solicited symptoms, non serious AEs within 43 days after Dose 1, Dose 2 and Dose 3 (in a subset) of study vaccine, by the investigator		•	•	•*		
Contact (field visit) every week	◊	◊	◊	◊	◊	◊
Return of GE diary	•	•	•	•*	•	•
GE diary transcription		•	•	•*	•	•
Documentation of routine EPI vaccines	•	•	•	•*	•	•
Recording medication	•	•	•	•*		
Reporting of SAEs occurring throughout the study period	•	•	•	•*	•	•
Study Conclusion					•¶	•§

Source: Protocol and sample eCRF in *Appendices: Study Information*
Notes: *Subset receiving three doses of HRV vaccine/placebo
◊ is used to indicate a study procedure which does not require documentation in the individual eCRFs
¶For subjects who participated only in the first efficacy follow-up period
§For subjects who participated in a second efficacy follow-up period

3.10 Subject completion and drop out

From an analysis perspective, a 'drop out' was any subject who did not come back for the concluding visit foreseen in the protocol. A subject who returned for the concluding visit foreseen in the protocol was considered to have completed the study.

Investigators attempted to contact those subjects who did not return for scheduled visits or follow-up. Information gathered was described on the Study Conclusion page of the eCRF and on Medication/AE forms. The possible reasons responsible for drop out of the subject from the study were specified on the Study Conclusion page of the eCRF and were as follows:

- SAE
- Non-serious AE
- Protocol violation (specify)
- Consent withdrawal, not due to an AE
- Migration from the study area
- Lost to follow-up
- Other (specify)

Study drop outs were not replaced.

3.11 Assessment of efficacy variables

An active surveillance for GE (defined as diarrhea) was conducted *via* weekly visit to each subject by study personnel (Health Workers) starting 1 week after Dose 1 of HRV vaccine or placebo and ending at the final study visit foreseen for that subject. All subjects were followed for efficacy until approximately one year of age. A subset of approximately 1000 subjects participated in the second efficacy follow-up period (until maximum age 24 months).

The weekly follow-up by the Health Worker took place at the subject's home, at a health clinic or other mutually convenient place. Health Workers inquired about occurrence of diarrhea at the weekly visits. Weekly visit by the Health Worker did not take place in weeks when a study clinic visit was scheduled.

The parents or guardians were instructed to contact study personnel whenever they suspected that the subject had diarrhea during the study. If diarrhea occurred during the solicited follow-up period (Day 0–Day 14 of each study vaccination), the information regarding the diarrhea episode was to be recorded on the reactogenicity diary card by the parents/guardians. If the diarrhea started during the solicited follow-up period and ended after the solicited follow-up period, the GE diary card was to be completed by the parents/guardians in addition to the reactogenicity diary card. The GE diary card was to be completed by the parents/guardians during each suspected episode of diarrhea that started outside the solicited follow-up period. On each day during a suspected episode of diarrhea, number of looser than normal stools, axillary/rectal temperature and number of vomiting episodes were recorded by the parents/guardians on the GE diary card until the end of the GE episode. Rehydration or other medications were also recorded. During weekly visits, the Health Worker ensured that the diary card was being properly completed and collected the completed diary cards. The investigator checked the completed diary cards and transcribed data into the appropriate sections of the eCRFs.

Parents/guardians of all subjects were instructed to collect one stool sample within 7 days of onset of each suspected diarrhea episode. A second stool sample was to be collected on a different day if the first stool sample was not sufficient. The time interval for stool sampling was adapted prior to analysis. Stool samples collected from the start of the GE episode to the minimum of the following 2 timepoints either 7 days after the end of the GE episode or the day before the next GE episode if subject had several episodes of GE were used to identify an episode of RV GE. Parents/guardians were given instructions to be followed for appropriate collection, storage and transportation of the stool samples. If required, Health Workers collected a stool sample during weekly visits. The Health Workers organized transportation of the stool samples.

Two occurrences of diarrhea were classified as separate episodes if there were 5 or more symptom-free days between the episodes.

A 20-point scoring system was used to assess the severity of each diarrheal episode ([4]). Refer to Table 4 for the scoring system used to assess the severity of each diarrhea episode using data collected *via* eCRFs.

Table 4: The 20-point scoring system used to assess the severity of each diarrhea episode

Adverse Experience	Points
Duration of looser than normal stools (days)	
1–4	1
5	2
≥ 6	3
Maximum number of looser than normal stools/24 hours	
1–3	1
4–5	2
≥ 6	3
Duration of vomiting (days)	
1	1
2	2
≥ 3	3
Maximum number of episodes of vomiting/24 hours	
1	1
2–4	2
≥ 5	3
Fever (measured rectally/axillary)*	
37.1–38.4°C/36.6-37.9°C	1
38.5–38.9°C/38.0-38.4°C	2
≥ 39°C/≥ 38.5°C	3
Treatment	
Rehydration	1
Hospitalization	2
Dehydration	
1–5 %	2
≥ 6%	3

Comments: * The highest temperature recorded during the episode was scored.

Points were assigned at GSK Biologicals according to duration and intensity of diarrhea and vomiting, the intensity of fever, presence of dehydration or hospitalization for each episode. Subjects with only fever or only vomiting did not receive a score.

A score of < 7 was prospectively defined as mild, a score of 7–10 was prospectively defined as moderate and a score ≥ 11 was prospectively defined as severe ([5]).

3.11.1 Diarrheal stool analysis

All stool samples collected during any episodes of diarrhea were analyzed locally using a commercially available rapid RV detection kit, RotaClone™ (Meridian Diagnostics Inc.). If RV was detected locally using RotaClone™ in a stool sample collected during the first efficacy follow-up period, an aliquot of the stool sample was analyzed locally for culture of enteric pathogens such as Salmonella, Shigella, and Campylobacter. Presence of Enteroaggregative *Escherichia coli* and Enteroinvasive *Escherichia coli* was tested at the laboratory of Dr. [redacted] Mexico.

All stool samples collected during any episodes of diarrhea, irrespective of results of the local RV (RotaClone™) tests, were tested centrally by Enzyme Linked Immunosorbent Assay (ELISA) ([1], [2]) at the Laboratory of Dr. [redacted] Children's Hospital Medical Centre, Cincinnati, USA to detect the presence of RV (refer to *Appendix C: Laboratory assays*). Only diarrheal stool analysis performed at the Laboratory of Dr. [redacted] Children's Hospital Medical Centre, Cincinnati, USA was considered for the efficacy analyses.

Efficacy estimates against severe RV GE were similar using locally-performed RotaClone™ test and centrally-performed ELISA test for detection of RV in stool samples. An overall agreement of 97% was also observed between the two RV detection methods.

All stool samples that were RV positive by centrally-performed ELISA were tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) at GSK Biologicals, Rixensart, Belgium to determine the G type (refer to *Appendix C: Laboratory assays*). If any G1 RV was detected in the stool samples collected between Visit 1 to Visit 3 (Visit 4 for subjects receiving three doses of HRV vaccine or placebo), vaccine virus was differentiated from wild-type RV by sequence analysis.

3.12 Assessment of safety variables

Pre-existing conditions, signs and/or symptoms (including any which were not recognized at study entry but were recognized during the study period) present in a subject prior to the start of the study were recorded on the Medical History Form within the subject's eCRF. AEs which occurred after informed consent was obtained, but prior to vaccination, were also documented in the Medical History Form within the subject's eCRF.

At each visit/assessment, all AEs either observed by the investigator or one of his clinical collaborators or reported by the subject spontaneously or in response to a direct question were evaluated by the investigator. AEs not previously documented in the study were recorded in the AE Form within the subject's eCRF. Details of any corrective treatment were recorded on the appropriate page of the eCRF. AEs already documented in the eCRF, i.e. at a previous assessment, and designated as 'ongoing' were reviewed at subsequent visits, as necessary. If these had resolved, the documentation in the eCRF was completed.

The parents/guardians were instructed to contact the investigator immediately if the subject manifested any signs or symptoms during the study that they perceived as serious.

Reactogenicity diary cards were distributed to the parents/guardians on the day of each study vaccination to record solicited AEs occurring during the 15-day (Day 0 to Day 14) solicited follow-up period. Intensity of the solicited AEs was assessed as described in Table 5.

Table 5: Intensity scales for solicited symptoms

Adverse Event	**Intensity grade**	**Parameter**
Diarrhea		Number of looser than normal stools/day recorded
Fever*		Temperature recorded rectally or axillary in °C
Irritability/fussiness	0	Behaviour as usual
	1	Crying more than usual/ no effect on normal activity
	2	Crying more than usual/ interferes with normal activity
	3	Crying that cannot be comforted/ prevents normal activity
Loss of appetite	0	Normal
	1	Eating less than usual/ no effect on normal activity
	2	Eating less than usual/ interferes with normal activity
	3	Not eating at all
Vomiting		Number of vomiting episodes/day recorded.
Cough/runny nose	0	Normal
	1	Cough/runny nose which is easily tolerated
	2	Cough/runny nose which interferes with daily activity
	3	Cough/runny nose which prevents daily activity

Comments: *Rectal /axillary temperature was recorded in the evening. If temperature measurement was performed additionally at another time of day, the highest temperature was recorded.

Health Workers ensured that the reactogenicity diary card was being properly completed by the parents/guardians, and collected the completed diary card. The investigator checked the completed diary cards and transcribed data into the appropriate sections of the eCRFs.

The maximum intensity of fever, diarrhea and vomiting were scored at GSK Biologicals as follows:

Diarrhea	0	:	0–2 looser than normal stools/day
	1	:	3 looser than normal stools/day
	2	:	4–5 looser than normal stools/day
	3	:	≥ 6 looser than normal stools/day

Fever			Measured rectally	Measured axillary
	0	:	< 38.0°C	< 37.5°C
	1	:	≥ 38.0 – ≤ 38.5°C	≥ 37.5 – ≤ 38.0°C
	2	:	> 38.5 – ≤ 39.5°C	> 38.0 – ≤ 39.0°C
	3	:	> 39.5°C	> 39.0°C

Vomiting	0	:	No emesis
	1	:	1 episode of vomiting/day
	2	:	2 episodes of vomiting/day
	3	:	≥ 3 episodes of vomiting/day

All other AEs occurring during the 43-day (Day 0 to Day 42) follow-up period after each vaccination were noted as unsolicited symptoms. Maximum intensity was assigned to one of the following categories:

1 : An AE which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2 : An AE which was sufficiently discomforting to interfere with normal everyday activities.

3 : An AE which prevented normal, everyday activities.
(Such an AE, for example, prevented attendance at school/kindergarten/day-care centre and caused the parents/guardians to seek medical advice.)

Every effort was made by the investigator to explain each AE and assess its causal relationship, if any, to administration of the study vaccine. The degree of certainty with which an AE could be attributed to administration of the study vaccines (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) was determined by how well the event could be understood in terms of one or more of the following:

- Reaction of similar nature having previously been observed with this type of vaccine and/or formulation.
- The event having often been reported in literature for similar types of vaccines.
- The event being temporally associated with vaccination or reproduced on re-vaccination.

Causality of all AEs was assessed by the investigator using the following question: In your opinion, did the vaccines possibly contribute to the AE?

NO : The AE was not causally related to administration of the study vaccine. There were other, more likely causes and administration of the study vaccine was not suspected to have contributed to the AE.

YES : There was a reasonable possibility that the vaccine contributed to the AE.

If an event met the criteria to be determined "serious" (see below for definition of serious adverse events (SAEs)), it was examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each SAE. Other possible contributors included:

- Medical history
- Other medication
- Protocol required procedure
- Lack of efficacy of the vaccine
- Erroneous administration
- Other cause (to be specified)

A SAE was defined as any untoward medical occurrence that:

- resulted in death
- was life threatening
- resulted in persistent or significant disability/incapacity
- required in-patient hospitalization or prolongation of hospitalization
- was a congenital anomaly/birth defect in the offspring of a subject

In addition, any important medical event that might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above was also considered as serious.

The investigator was required to notify GSK Biologicals of any SAE starting from the day of administration of the first dose of HRV vaccine or placebo to each subject and ending at study end, within 24 hours of his/her becoming aware of the event. Following the telephone report, a full written report was to be provided which included all relevant supporting documentation such as hospital records, eventual post-mortem reports and/or other documents where applicable. The standard verbal autopsy questionnaire was to be completed and transmitted by the investigator or his designee, in addition to the SAE report, for all deaths during the study period irrespective of relationship to vaccination and whether a written autopsy report was available or not.

Parents/guardians were informed about symptoms consistent with IS namely severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41° C and made aware that there could be possible increased risk of IS after vaccination. Parents/guardians were asked to contact the investigator if they noticed any symptoms indicative of IS. The investigator and his staff were also aware of the possible increased risk of IS and considered this diagnosis in children presenting symptoms indicative of IS. In case a subject was diagnosed with IS, immediate reporting to the sponsor was mandatory as for any SAE. The diagnosis of IS was to be documented by radiography. Detailed instructions on the evaluation of IS were provided to the investigator and his staff. The investigator was to take appropriate actions to evaluate and treat the condition. The investigator was required to document all available information for each IS case on the SAE pages in the eCRF. In addition, the investigator was required to complete the IS Form when all data became available and fax it to the GSK contact for SAE reporting. Each case of suspected or confirmed IS was reviewed by the IDMC.

Treatment of any AE was at the discretion of the investigator and according to current GCP. Treatment measures were reported in the appropriate pages of the eCRF. The investigator was to follow subjects with SAEs until the event subsided or until the condition stabilized. The investigator was to follow subjects with non-serious AEs until study conclusion for that subject.

The outcome of all AEs, non-serious and serious, was indicated as follows:
1: Recovered
2: Recovered with sequelae
3: Ongoing at subject study conclusion
4: Died
5: Unknown

3.12.1 Pregnancy

Not applicable.

3.12.2 Prior and concomitant medication

The investigator questioned the parents/guardians about any medication given to the subject at Visits 1, 2 and 3 (for all subjects) and at Visit 4 (for the subset receiving three doses of HRV vaccine or placebo).

Administration of the following treatments was recorded in the eCRF by the investigator if the medication was given within the specified time frames:

- Any immunosuppressants or other immune-modifying drugs or treatments administered at any time during the period starting 30 days prior to the first dose of HRV vaccine or placebo and ending at Visit 3 (Visit 4 for the subset receiving three doses of HRV vaccine or placebo).
- Any vaccine other than the study vaccine(s) administered at any time during the period starting at birth and ending at the last study visit.
- Any antibiotics administered within 7 days preceding each study vaccine/placebo administration and during the first 7 days after each study vaccine/placebo administration.
- Any antipyretics administered at any time during the period starting 30 days prior to the first dose of HRV vaccine or placebo and ending one month (minimum 30 days) after the last dose of HRV vaccine or placebo.

Any other concomitant medication administered prophylactically in anticipation of reaction to the vaccination were also recorded in the eCRF with trade name and/or generic name of the medication, total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'.

3.13 Assessment of immunogenicity variables

3.13.1 Intervals between study visits

To adequately assess the immune responses elicited by the vaccines, time intervals to be respected between visits for vaccination and blood sampling were detailed in the protocol (see Table 6 and Table 7).

Table 6: Intervals between study visits for subjects planned to receive two doses of HRV vaccine or placebo*

Interval	Size of interval
Visit 1→Visit 2	49– 83 days
Visit 2→Visit 3	49–83 days
Visit 3→Follow-up visit at the end of the first efficacy follow-up period	160–200 days

Comments: * = Date of the previous visit was the reference date.

Table 7: Intervals between study visits for subjects receiving three doses of HRV vaccine or placebo*

Interval	Size of interval
Visit 1→Visit 2	49–83 days
Visit 2→Visit 3	49–83 days
Visit 3→Visit 4	49–83 days
Visit 3→Follow-up visit at the end of the first efficacy follow-up period	160–200 days

Comments: * = Date of the previous visit was the reference date

Subjects outside the protocol-specified intervals between Visit 1–2 and Visit 2–3 were excluded from the ATP cohort for immunogenicity analysis for subjects planned to receive two doses of HRV vaccine or placebo (immunogenicity analysis performed only on the total vaccinated cohort for subjects receiving three doses of HRV vaccine or placebo).

3.13.2 Laboratory assays and timepoints

3.13.2.1 Stool analysis

For subjects planned to receive two doses of HRV vaccine or placebo: Stool samples were collected on the day of Dose 1 and Dose 2 and on Day 7±1 after Dose 1 and Dose 2 of HRV vaccine or placebo from stool analysis subset in subjects planned to receive two doses of HRV vaccine or placebo.

For subjects receiving three doses of HRV vaccine or placebo: Stool samples were collected on the day of Dose 3 and on Day 7±1 after Dose 3 of HRV vaccine or placebo from all subjects who received a third dose of HRV vaccine or placebo.

All stool samples collected at pre-determined timepoints were analyzed using ELISA to detect RV at the Laboratory of Dr. [redacted] Children's Hospital Medical Centre, Cincinnati, USA (refer to *Appendix C: Laboratory assays*).

If RV was detected in stool samples collected at pre-determined timepoints from subjects in the placebo group, G type was determined *post-priori* by RT-PCR at GSK Biologicals, Rixensart, Belgium.

Any detection of RV in stool collected after each vaccination at pre-determined time points was taken as evidence of a vaccine response (i.e. vaccine take), as long as the subject is negative for RV on the day of Dose 1 of HRV vaccine or placebo.

Stool samples were also collected from all subjects during each diarrheal episode occurring during the study period. Refer to Section 3.11.1 for analysis of diarrheal stool samples.

3.13.2.2 Serum analysis

For subjects planned to receive two doses of HRV vaccine or placebo:

A minimum of 1 ml of whole blood was collected from all subjects at Visit 1 (on the day of Dose 1 of HRV vaccine or placebo) to test for anti-rotavirus IgA antibodies.

Whole blood samples were collected from a subset of 800 subjects on the day of Dose 2 of HRV vaccine or placebo at Visit 2 (1 ml of whole blood to test for anti-rotavirus IgA antibodies), two months after Dose 2 of HRV vaccine or placebo at Visit 3 (3 ml of whole blood to test for anti-rotavirus IgA antibodies and antibodies to concomitant DTPw-HB+Hib vaccination and OPV) and at the end of the first efficacy follow-up period (3 ml of whole blood to test for anti-rotavirus IgA antibodies and antibodies to concomitant DTPw-HB+Hib vaccination and OPV).

A minimum of 1 ml of whole blood was collected from all other subjects at the end of the first efficacy follow-up period to test for anti-rotavirus IgA antibodies.

For subjects receiving three doses of HRV vaccine or placebo: Whole blood samples were collected at Visit 1 and on the day of Dose 3 of HRV vaccine or placebo at Visit 3 (1 ml of whole blood to test for anti-rotavirus IgA antibodies only), and two months after Dose 3 of HRV vaccine or placebo at Visit 4 (3 ml of whole blood to test for anti-rotavirus IgA antibodies and antibodies to concomitant DTPw-HB+Hib vaccination and OPV). Antibodies to DTPw-HB+Hib and OPV vaccines were planned to be measured only at Visit 4 but were also measured at Visit 3.

All blood samples were centrifuged, separated locally and shipped to the laboratories where serum analyses were performed. All serum samples were stored at –20°C and the following serological tests were performed.

Serum anti-rotavirus IgA antibody concentrations were measured by ELISA at the Laboratory of Dr. [redacted] Children's Hospital Medical Centre, Cincinnati, USA and expressed in units per milliliter (U/ml) (refer to *Appendix C: Laboratory assays*). The assay cut-off was 20 U/ml. The ELISA test for anti-rotavirus antibodies uses the "sandwich principle". A solid phase enzyme-linked immunoassay technique is used to detect human anti-rotavirus IgA levels in serum. The assay used was based on the assay previously described by Dr. R. Ward and his co-workers ([6]). The limit of detection of the assay was 5.4 U/ml, whereas the limit of quantification (= the lowest concentration that could be reliably measured) was 13.4 U/ml. Therefore, the technical cut-off has been set at 20 U/ml as a theoretically and practically meaningful value.

A seronegative subject for anti-rotavirus IgA antibodies was defined as a subject who had antibody concentration below the assay cut-off value. A seropositive subject for anti-rotavirus IgA antibodies was defined as a subject who had antibody concentration greater than or equal to the assay cut-off value.

A subject initially negative for RV was defined as a subject who was negative for anti-rotavirus IgA antibodies in serum and for RV antigen in a stool sample at a pre-vaccination time point, if both results were available, or negative for at least one of these markers if only one result was available.

Antibodies against antigens contained in concomitantly administered routine DTPw-HB+Hib vaccines and OPV were tested using standard serological assays as specified in Table 8.

Table 8: Serological assays for antibodies to concomitantly administered routine vaccinations

Antibody	Assays Method	Test Kit manufacturer	Assay Cut-off	Assay units	Laboratory
Anti-diphtheria	ELISA([7])	In-house	0.1	IU/ml	[redacted] Lab
Anti-tetanus	ELISA([8])	In-house	0.1	IU/ml	[redacted] Lab
Anti-BPT	ELISA	In-house	15	EL.U/ml	GSK Rix
Anti-HBs	ELISA	In-house	10	mIU/ml	[redacted] Lab
Anti-PRP	ELISA	In-house	0.15	mcg/ml	[redacted] Lab
Anti-poliovirus type 1	Neutralization	In-house	1:8	dilution titer	[redacted] Lab
Anti-poliovirus type 2	Neutralization	In-house	1:8	dilution titer	[redacted] Lab
Anti-poliovirus type 3	Neutralization	In-house	1:8	dilution titer	[redacted] Lab

Notes: IU = Internation Units
EL.U = Elisa Units
mIU = milli International Units
Comments: [redacted] Lab = Laboratory of Dr. [redacted] University of Rochester, USA
GSK Rix = GlaxoSmithKline Biologicals, Rixensart, Belgium

If there was insufficient serum sample volume to perform assays for all antibodies, tests were performed according to the following priority ranking specified in the protocol: anti-rotavirus IgA, anti-PRP, anti-HBs, anti-diphtheria, anti-tetanus, anti-BPT, anti-poliovirus type 1, anti-poliovirus type 2 and anti-poliovirus type 3.

3.14 Data quality assurance

To ensure that study procedures conformed across all study centres, the protocol, eCRFs and safety reporting procedures were reviewed with the investigators and their personnel responsible for the conduct of the study by the GSK Biologicals representatives at the study sites prior to study start.

Adherence to the protocol requirements and verification of data generation accuracy was achieved through monitoring visits to each investigator site. Computer checks and blinded review of subject tabulations were performed to ensure consistency of eCRF completion. All procedures were performed according to methodologies detailed in GSK Biologicals' Standard Operating Procedures.

There were no major findings affecting the outcome of the procedures applied for testing with RotaClone™ during audits of local laboratories conducted by GSK Biologicals. The local laboratory personnel were coached to implement a full Quality System and maintain appropriate documentation.

There were no major findings affecting the outcome of microbiological co-pathogen testing during audits of local laboratories conducted by GSK Biologicals. Supplementary Quality Control checks and appropriate documentation were implemented at the local laboratories.

Independent Audit statement:
This study was subject to two audits by GSK's department of Worldwide Regulatory Compliance-GCP (WRC-GCP). The WRC-GCP conducted routine compliance audits at the Venezuelan study centre (27–28 February, 2002) and the Brazilian study centre (25–26 September, 2002). There were no critical or major observations identified during both audits.

3.15 Statistical methods

Statistical analyses to be performed were planned and described in the study protocol. All performed analyses, including any additional analyses, are detailed in the Project and Study Report Analysis Plans. The Report Analysis Plans were prepared and finalized before the database was frozen for the analysis at the end of the first efficacy follow-up period.

The analyses were performed using SAS 8.2 and Proc StatXact-5 on Windows NT 4.0.

Note: Although all study endpoints are listed, only analyses of data obtained until the end of the first efficacy follow-up period are presented in this report.

3.15.1 Primary endpoint

For the subset of subjects planned to receive two doses of HRV or placebo:

- Occurrence of any RV GE during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period.

3.15.2 Secondary endpoints

Efficacy endpoints

For the subset of subjects planned to receive two doses of HRV or placebo:

- Occurrence of severe RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of RV GE due to virus types heterologous to vaccine strain during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of any and severe pure RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of RV GE in which there is at least one other pathogen during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of hospitalization for RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.

For the subset of subjects who received three doses of HRV or placebo:

- Occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 3 until the end of the first efficacy follow-up period.

For the subset of subjects who participated in the second efficacy follow-up period until maximum age 24 months:

- For the subset of subjects who received two doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.
- For the subset of subjects who received two doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the second efficacy follow-up period.
- For the subset of subjects who received three doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.
- For the subset of subjects who received three doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 3 until the end of the second efficacy follow-up period.

Safety endpoints

- For each type of solicited symptoms, occurrence of the symptom within the 15-day solicited follow-up period after any dose of study vaccine (in a subset after Dose 3).

- Occurrence of unsolicited symptoms within 43 days (Day 0–Day 42) after Dose 1, Dose 2 (in all subjects) and Dose 3 (in a subset), according to World Health Organization (WHO) classification.
- Occurrence of SAEs throughout the entire study period.

Immunogenicity endpoints

For the subset of subjects planned to receive two doses of HRV or placebo:

- Serum anti-rotavirus IgA antibody concentrations at Visit 1 and the end of the first efficacy follow-up period in all subjects and at Visits 2 and 3 in a subset of subjects.
- Proportion of subjects with vaccine take at Visits 2 and 3 in the stool analysis subset.
- Vaccine take and GMCs of RV IgA ELISA calculated in a subset for breast-fed infants compared with formula fed infants for the following 3 categories: 1) whether the infant received no food 1 hour prior to and 30 minutes after Dose 1 or Dose 2 (as reported by the mother); 2) whether the infant received food 1 hour prior to Dose 1 or Dose 2 (as reported by the mother); and 3) whether the infant received food within 30 minutes after Dose 1 or Dose 2.
- Viral shedding in the vaccine groups in the stool analysis subset.

Two months after Dose 2 (at Visit 3) and at Year 1 in a subset of subjects:

- GMC/Ts for anti-PRP, anti-diphtheria, anti-tetanus, anti-BPT, anti-poliovirus types 1, 2 and 3, and anti-HBs antibodies.
- Seroprotection status:
  - ◊ anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
  - ◊ anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-HBs antibody concentrations ≥ 10 mIU/ml
  - ◊ anti-poliovirus type 1 antibody titers ≥ 8
  - ◊ anti-poliovirus type 2 antibody titers ≥ 8
  - ◊ anti-poliovirus type 3 antibody titers ≥ 8
- Seropositivity status:
  - ◊ anti-BPT antibody concentrations ≥ 15 EL.U/ml

For the subset of subjects who received three doses of HRV or placebo:

- Serum anti-rotavirus IgA antibody concentrations at Visits 1, 3 and 4.
- GMC/Ts for anti-PRP, anti-diphtheria, anti-tetanus, anti-BPT, anti-poliovirus types 1, 2 and 3, and anti-HBs antibodies two months after Dose 3.
- Seroprotection status two months after Dose 3:
  - ◊ anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
  - ◊ anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml

  - ◊ anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-HBs antibody concentrations ≥ 10 mIU/ml
  - ◊ anti-poliovirus type 1 antibody titers ≥ 8
  - ◊ anti-poliovirus type 2 antibody titers ≥ 8
  - ◊ anti-poliovirus type 3 antibody titers ≥ 8
- Seropositivity status two months after Dose 3:
  - ◊ anti-BPT antibody concentrations ≥ 15 EL.U/ml
- Viral shedding in the vaccine groups on the day of and on Day 7 after Dose 3.

3.15.3 Determination of sample size

The target sample size was planned at 2640 enrolled subjects to reach 2360 subjects (590 per group) in the ATP cohort for efficacy analysis to evaluate the primary objective. However, the target sample size was reduced to 2276 subjects in the amendment 3 dated May 3, 2002 because of difficulty in enrolling eligible subjects for participation in the study. Amendment 3 dated May 3, 2002 also planned that 200 of the 2276 subjects were to receive a third dose of HRV vaccine or placebo.

Thus, the final eligible sample size for analysis of the primary efficacy objective was to be 2076 eligible subjects (460 evaluable subjects per group) to receive two doses of HRV vaccine or placebo for the analysis of the primary objective.

The anticipated attack rate in the placebo for any RV GE was 12%. However, with the observed attack rate of 10.8% for any RV GE in the placebo, and assuming vaccine efficacy of 70%, sample size of 2076 eligible subjects provided more than 82% power that the lower limit (LL) of the 95% Confidence Intervals (CIs) for efficacy against any RV GE during the first efficacy follow-up period is above 30% (see Table 9). With this sample size of 2076 subjects and the observed attack rate, the study was still sufficiently powered to evaluate the study objectives and draw conclusions.

The sample size justification was done by calculating the power using different efficacy estimates for a vaccine group and for a range of attack rates of any RV GE (primary endpoint) and severe RV GE (secondary endpoint) in the placebo as shown in Table 9. Power was higher for the evaluation of efficacy on pooled HRV.

Table 9: Power to get an exact 95% CI for the vaccine efficacy for a vaccine group above a specific cut-off (N = 460 subjects by group, power based on 1.000 simulations using Proc StatXact) (Refer to Appendix B for mathematical details)

% of subjects reporting RV GE in the placebo group from two weeks after Dose 2 until the end of the efficacy follow-up period following vaccination	**% of subjects reporting RV GE in the vaccine group from two weeks after Dose 2 until the end of the efficacy follow-up period following vaccination**	**Efficacy (%)**	**Cut-off (LL of 95% CI for vaccine efficacy)**			
			0%	10%	20%	30%
Any RV GE			**Power that the LL is above each cut-off**			
12%*	3.6%	70%	99.7%	99.2%	97%	88.9%
12%*	4.8%	60%	96.8%	92.0%	81.8%	58.1%
12%*	6 %	50%	84.1%	71.1%	48.8%	26.7%
10%	3%	70%	98.8%	97.4%	92.4%	82.2%
10%	4%	60%	93.5%	84.8%	71.4%	51.2%
10%	5%	50%	77.4%	61.7%	41.4%	20.5%
Severe RV GE						
4%*	0.8%	80%	89%	84%	76%	
4%*	1%	75%	80%	74%	63%	
4%*	1.2%	70%	72%	62%	50%	
3%	0.6%	80%	75%	68%	61%	
3%	0.75%	75%	63%	52%	44%	
3%	0.9%	70%	56%	45%	37%	

Comment: *anticipated incidence rate

The analysis looked at the pooled vaccine groups *versus* placebo and each vaccine group *versus* placebo.

In order to control the risk of falsely concluding below 5%, the primary objective was addressed using a hierarchical testing. Pooled HRV vaccine group was first tested and, only if efficacy was demonstrated, the vaccine with a viral concentration of $10^{5.8}$ ffu was tested. Likewise, only if efficacy of vaccine with a viral concentration of $10^{5.8}$ ffu was demonstrated, the vaccine with a viral concentration of $10^{5.2}$ ffu was tested. Likewise, only if efficacy of vaccine with a viral concentration of $10^{5.2}$ ffu was demonstrated, the vaccine with a viral concentration of $10^{4.7}$ ffu was tested. Efficacy was established if the percentage of subjects with RV GE during the period starting from 2 weeks after Dose 2 of HRV vaccine or placebo until the end of the efficacy follow-up period following vaccination in the HRV vaccine group was statistically significantly lower than in the placebo group (two-sided Fisher Exact test: $p < 0.05$).

It should be noted that only 121 subjects of the planned 200 received a third dose of HRV vaccine or placebo. Therefore, the final eligible sample size for analysis of the primary objective was 2155 subjects.

The size of the subset to be followed during the second efficacy follow-up period was based on the assumption that the attack rate of any RV GE would be 12% in the placebo group. Assuming 60% vaccine efficacy, a subset of 200 subjects in each group was estimated to provide 88% and 67% power to detect a statistically significant vaccine effect with the pooled HRV vaccine group and each vaccine group, respectively (2 sided Fisher's exact test, alpha = 5%, no adjustment for multiplicity). Thus, a subset of approximately 1000 subjects who had not completed the study as of October 31, 2002 participated in the second efficacy follow-up period until maximum 24 months of age.

The size of the subset to assess the immunogenicity of the concomitant routine vaccinations and OPV was based on the assumption that seroprotection rates would be between 90% and 98% (for anti-diphtheria, anti-tetanus, anti-PRP, anti-HBs and anti-poliovirus types 1, 2 and 3 antibodies) and anti-BPT Geometric Mean Concentration (GMC) would be 27.3 EL.U/ml (with a standard deviation of 0.332) (reference study: DTPw-HBV-Hib-003), and assuming that the rates/GMC/GMT would be the same in the vaccine and placebo groups. A subset of 175 evaluable subjects per group was estimated to provide 80% global power to show that all the 95% CI on the decrease in seroprotection rates in the HRV vaccine group as compared to the placebo group are below 15% and that the 95% CIs on the fold decrease in anti-BPT GMCs in the HRV vaccine group as compared to the placebo group is below 1.5 (power based on 1000 simulations with proc StatXact for the difference in seroprotection rates and using Nquery for the ratio of anti-BPT GMCs, one sided equivalence test, alpha = 2.5%). Allowing for up to 12% of subjects who may not be evaluable for the immunogenicity analysis, blood samples were taken from approximately 200 subjects per group to assess immunogenicity of concomitant routine vaccinations and OPV. This power calculation was done for analyses at approximately 6 months after completion of the routine three-dose primary vaccination course (at the end of the first efficacy follow-up period). However, immunogenicity of routine vaccinations was also analysed at two months after Dose 2 of HRV vaccine or placebo (which corresponds to Dose 2 of routine vaccinations).

An amendment dated May 3, 2002 allowed administration of a third dose of the HRV vaccine or placebo to a subset of infants following the interim immunogenicity analysis performed in March 2002. A subset of approximately 200 subjects from Brazil and Venezuela who had not completed Visit 3 at the time of the amendment were planned to receive a third dose of HRV vaccine or placebo at Visit 3. The amendment was not approved in Venezuela, and therefore only 121 subjects from Brazil were part of the subset receiving a third dose HRV vaccine or placebo. Only descriptive analyses were performed on the data from the subset receiving three doses of HRV vaccine or placebo.

3.15.4 Study cohorts/data sets analyzed

The following subject cohorts were evaluated:

Total vaccinated cohort
The total vaccinated cohort included all subjects with at least one study vaccine administration documented:

- Safety analysis based on the total vaccinated cohort included all vaccinated subjects.
- Immunogenicity analysis based on the total vaccinated cohort included all vaccinated subjects for whom immunogenicity data were available.
- Efficacy analysis based on the total vaccinated cohort for the subset of subjects planned to receive two doses of HRV or placebo included all vaccinated subjects for whom efficacy follow-up data were available. Efficacy follow-up was derived from any contact
    - beyond 2 weeks after the second dose of HRV vaccine or placebo for the first efficacy follow-up period.
- Efficacy analysis based on the total vaccinated cohort for the subset receiving three doses of HRV vaccine or placebo included all vaccinated subjects for whom efficacy follow-up data were available. Efficacy follow-up was derived from any contact
    - beyond 2 weeks after the third dose of HRV vaccine or placebo for the first efficacy follow-up period.

ATP cohort for safety analysis
The ATP cohort for safety analysis included all subjects:

- who had received at least one dose of HRV vaccine or placebo according to the randomization list,
- for whom the randomization code had not been broken by the investigator,
- who had not received a vaccine forbidden by or not specified in the protocol,

- for whom the HRV vaccine or placebo was administered according to the protocol, (Note: subjects who regurgitated within 30 minutes after vaccination were eliminated for this reason)
- who had not received a replacement vial, except if the appropriate vaccine was administered in "double-blind replacement",
- who were negative for RV antigen on the day of Dose 1 of HRV vaccine or placebo.

ATP cohort for immunogenicity analysis
The ATP cohort for immunogenicity analysis included all subjects from the ATP safety cohort:
- who had not received medication forbidden by the protocol,
- whose underlying medical condition was not forbidden by the protocol,
- with no protocol violation of demographics (unknown age at study entry or outside protocol defined age-interval),
- who complied with vaccination schedule,
- who complied with blood sampling schedule,
- who had no RV other than vaccine strain in stool samples collected during the vaccination period (from Visit 1 to Visit 3),
- who had no concomitant infection unrelated to the vaccine which may influence the immune response.
- for whom post results (for anti-rotavirus IgA antibodies or for stool) were available at least one post-vaccination timepoint up to the end of the first efficacy follow-up period.

ATP cohort for efficacy analysis
The ATP cohort for efficacy analysis for the first efficacy follow-up period included all subjects from the ATP safety cohort:
- who received 2 doses of HRV vaccine or placebo,
- who had no RV other than vaccine strain in stool samples collected between the day Dose 1 of HRV vaccine or placebo was administered and 2 weeks after Dose 2 of HRV vaccine or placebo was administered,
- who had entered into the surveillance period: had follow-up beyond 2 weeks after Dose 2 of HRV vaccine or placebo.

Datasets analyzed
For the subset planned to receive two doses of HRV vaccine or placebo
The total vaccinated cohort was used for the primary analysis of safety. The analysis on the ATP cohort for safety was to be performed only if more than 5% of the enrolled subjects were excluded from the ATP safety cohort.

Analysis of efficacy during the first efficacy follow-up period was performed on the ATP cohort (primary analysis) and the total vaccinated cohort.

The ATP immunogenicity cohort was used for the primary analysis of immunogenicity. An analysis of immunogenicity based on the total vaccinated cohort was to be performed only if more than 5% of the enrolled subjects were excluded from the ATP immunogenicity cohort. In such a case, the analysis on the total vaccinated cohort evaluated whether exclusion from the ATP cohort had biased the results.

Subjects excluded from the ATP cohorts were identified before data analysis after a review of the individual subject data blinded to group allocation.

For the subset receiving three doses of HRV vaccine or placebo
The analyses of safety, efficacy and immunogenicity were performed only on the total vaccinated cohort.

3.15.5 Analysis of demographics

3.15.5.1 For the subset planned to receive two doses of HRV vaccine or placebo

Demographic characteristics (age, height and weight descriptive statistics, and gender and race distribution) at Visit 1 were tabulated by group for the ATP cohort for efficacy analysis, the ATP cohort for immunogenicity analysis and the total vaccinated cohort. For the total vaccinated cohort, this analysis was also done by country.

The height and weight increases at each visit were tabulated for the total vaccinated cohort.

Summary of feeding criteria on the day of each study vaccination was presented by group for the ATP cohort for immunogenicity analysis.

The percentages of subjects who received OPV at birth were tabulated for the ATP cohort for immunogenicity analysis.

3.15.5.2 For the subset receiving three doses of HRV vaccine or placebo

Demographic characteristics (age, height and weight descriptive statistics, and gender and race distribution) at Visit 1 were tabulated by group for subjects included in the total vaccinated cohort.

The height and weight increases at each visit were tabulated for the total vaccinated cohort.

Summary of feeding criteria on the day of each study vaccination was presented by group for the total vaccinated cohort.

3.15.6 Analysis of efficacy

3.15.6.1 Efficacy during first efficacy follow-up period for the subset planned to receive two doses of HRV vaccine or placebo

The first efficacy follow-up period started from two weeks after Dose 2 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age).

All calculations were done for each study group and for pooled HRV vaccine groups.

The duration of the efficacy follow-up period was tabulated by group.

A global overview of the number of GE episodes of any etiology (RV or not) and RV GE episodes during the first efficacy follow-up period was provided by severity. A summary of RV GE episodes reported during the first efficacy follow-up period by type was provided.

The percentages of subjects with any and severe RV GE (all RV types, by RV type and by country) and percentages of subjects hospitalized due to RV GE during the first efficacy follow-up period were calculated with their 95% CI. Two-sided Fisher's exact test (significance level of α=0.05) was used to compare these percentages between vaccine groups and placebo.

Proportion of pure RV GE and mixed RV GE cases was evaluated by calculating the proportion of RV GE episodes with concurrent presence of at least one other pathogen.

The percentages of subjects reporting at least one RV GE episode during the first efficacy follow-up period according to the serological status for IgA antibodies at two months after Dose 2 of HRV vaccine or placebo were computed.

Efficacy of the HRV vaccine during the first efficacy follow-up period was calculated with its 95% CI against

- any and severe RV GE
- any and severe RV GE by RV type
- hospitalization due to RV GE

Vaccine efficacy, with 95% CI, against any and severe RV GE was also calculated by country.

Vaccine efficacy was defined as the percent reduction in the frequency of the considered endpoint in vaccinated subjects compared with those subjects who received placebo.

The vaccine efficacy was calculated using the formula: 1 – RR = 1 – (ARV/ARU)

RR = relative risk = ARV/ARU

- ARU = disease attack rate in unvaccinated population (estimated from the placebo group) = nu/Nu = number of subjects reporting at least one RV GE episode / total number of subjects in the placebo (control) group.
- ARV = disease attack rate in vaccinated group = nv/Nv = number of subjects reporting at least one RV GE episode / total number of subjects in the HRV vaccine group.

The 95% CIs for vaccine efficacy were derived using a conditional to cases approach (refer to *Appendix B: Mathematical details about the computation of the 95% CI for vaccine efficacy*).

To check the robustness with respect to the statistical analysis, vaccine efficacy against the primary endpoint (occurrence of any RV GE from 2 weeks after Dose 2 of HRV vaccine or placebo until the end of the efficacy follow-up period) and its 95% CI were also estimated by the Cox proportional-hazard model including the group effect as regressor. The Kaplan Meier survival curves were generated to analyze the time from 2 weeks after Dose 2 of HRV vaccine or placebo to the onset of RV GE. The time was censored at the last contact in the first efficacy follow-up period.

In addition, person-year rates of any and severe RV GE (all RV types and by RV type), hospitalization due to RV GE and any and severe RV GE by country within each group were assessed using a loglinear Poisson model.

In order to control the risk of falsely concluding below 5%, the primary objective (prevention of any RV GE from 2 weeks after Dose 2 of HRV vaccine or placebo until the end of the efficacy follow-up period) was assessed using a hierarchical testing. Pooled HRV vaccine group was tested first and, only if efficacy was demonstrated, Group $10^{5.8}$ ffu HRV was tested. Likewise, only if efficacy of Group $10^{5.8}$ ffu HRV was demonstrated, Group $10^{5.2}$ ffu HRV was tested. Likewise, only if efficacy of Group $10^{5.2}$ ffu HRV was demonstrated, Group $10^{4.7}$ ffu HRV was tested. Efficacy was established if the percentage of subjects with RV GE during the period starting from 2 weeks after Dose 2 of HRV vaccine or placebo until the end of the efficacy follow-up period following vaccination in the HRV vaccine group was statistically significantly lower than in the placebo group (two-sided Fisher's Exact test: $p < 0.05$).

In order to have a first look at the effectiviness of the vaccine from the first dose onwards, occurrence of RV GE episodes from Day of Dose1 till Day 14 of Dose 2 and occurrence of RV GE episodes from Day of Dose1 till the end of the first efficacy follow-up period were evaluated. These analyses were performed only on the total vaccinated cohort. The percentages of subjects with any and severe RV GE from Day of Dose1 till Day 14 of Dose 2 and from Day of Dose1 till the end of the first efficacy follow-up period were calculated by groups and for pooled HRV groups, with their 95% CI. Two-sided Fisher's exact test (significance level of α=0.05) was used to compare rates between vaccine groups and placebo for the period starting from Day of Dose1 till the end of the first efficacy follow-up period. Vaccine efficacy, with 95% CI, was calculated against any and severe RV GE occurring from Day of Dose1 till Day 14 of Dose 2 and against any and severe RV GE occurring from Day of Dose1 till the end of the first efficacy follow-up period.

3.15.6.2 Exploratory efficacy during the first efficacy follow-up period for the subset receiving three doses of HRV vaccine or placebo

The first efficacy follow-up period started from two weeks after Dose 3 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age).

The percentages of subjects with RV GE (any and severe intensity) from two weeks after Dose 3 of HRV vaccine or placebo until the end of the first efficacy follow-up period were calculated with their exact 95% CI.

3.15.7 Analysis of safety

Solicited symptoms were recorded during the 15-day (Day 0 to Day 14) solicited follow-up period after each study vaccination. Unsolicited symptoms were recorded during the 43-day (Day 0 to Day 42) follow-up period after each study vaccination. SAEs were recorded during the entire study period.

3.15.7.1 Reactogenicity of two doses of HRV vaccine and placebo

The following calculations were performed for each study group and for pooled HRV vaccine groups:

The percentages of doses and of subjects reporting at least one AE (solicited or unsolicited) during the solicited follow-up period were computed, along with exact 95% CI. The same calculations were done for symptoms rated as grade "3" in intensity and for symptoms assessed as related to vaccination. These calculations were also done by country.

The percentages of doses and of subjects reporting specific solicited symptoms were calculated, with exact 95% CI, over the solicited follow-up period (Day 0 to Day 14). The same calculations were done for solicited symptoms rated as grade "2 or 3" in intensity, rated as grade "3" in intensity and for solicited symptoms assessed as related to vaccination. These calculations were also done by country.

Pair-wise differences among the three HRV vaccine groups and between the pooled HRV vaccine group and the placebo group were explored using the two-sided Fisher's exact test for the endpoints mentioned below. Statistically significant differences (p-value < 0.05) should be interpreted cautiously since, due to the number of endpoints, the differences observed in this study are likely to occur by chance alone.

- percentage of subjects reporting each individual solicited symptom within the 15-day (Days 0 to Day 14) follow-up period after any dose of HRV vaccine or placebo.
- percentage of subjects reporting each individual solicited symptom within the 8-day (Days 0 to Day 7) follow-up period after any dose of HRV vaccine or placebo.
- percentage of subjects reporting each individual grade "3" solicited symptom within the 8-day (Days 0 to Day 7) follow-up period after any dose of HRV vaccine or placebo.
- percentage of subjects reporting each individual grade "2 or 3" solicited symptoms within the 8-day (Days 0 to Day 7) follow-up period after any dose of HRV vaccine or placebo.
- percentage of subjects reporting each individual solicited symptoms assessed as related to vaccination within the 8-day (Days 0 to Day 7) follow-up period after any dose of HRV vaccine or placebo.

Prevalence of diarrhea, vomiting and fever by day during the solicited follow-up period were displayed graphically, by group. Prevalence is the percentage of subjects who reported the event at a certain (fixed) time point among doses administered.

Descriptive statistics for duration of diarrhea, vomiting and fever during the solicited follow-up period by dose and for overall doses were tabulated. Missing value at a specific day was considered as absence of the symptom on that day.

The verbatim reports of unsolicited symptoms were coded by use of the WHO's Dictionary for Adverse Reaction Terminology; every verbatim term, as stated by the reporter, was matched to the appropriate WHO Preferred Term associated to the symptom. The percentage of subjects and of doses reporting unsolicited symptoms classified by WHO body system/WHO Preferred Terms within 43 days (Day 0–Day 42) after vaccination were tabulated, with exact 95% CI. Similar tabulations were also done for unsolicited symptoms rated as grade "3" in intensity and those assessed as related to vaccination. These tabulations were also done by country.

The percentage (with exact 95 % CI) of subjects and doses reporting gastrointestinal symptoms (WHO code 600) including those graded "3" in intensity and those considered to be related to vaccination, within 43 days (Day 0–Day 42) after vaccination were tabulated.

The percentages of subjects who took at least one concomitant medication during the solicited follow-up period (Day 0–Day 14 after vaccination) were tabulated by type of medication. The prevalence of subjects who took antipyretics from Day 0 to Day 42 after vaccination was displayed graphically.

The number of SAEs occurring until the end of the first efficacy follow-up period were reported. SAEs assessed as possibly related to vaccination, SAEs with fatal outcome and IS cases were described. There may be minor discrepancies in the details of the SAEs included in the clinical narratives compared with the safety tabulations. This is because the data came from two different databases using different classifications [WHO/ Medical Dictionary for Regulatory Activities (MedDRA)] and was collected at different points in time. However, it was considered that these differences, if any were minor in nature and do not change the overall clinical significance or understanding of the SAE.

3.15.7.2 Reactogenicity of HRV vaccine and placebo in the subset receiving three doses of HRV vaccine or placebo

All descriptive analysis described in Section 3.15.7.1, except duration and prevalence of diarrhea, vomiting and fever during the solicited follow-up period and incidence of unsolicited gastrointestinal symptoms, were performed on reactogenicity and safety data obtained in the subset receiving three doses of HRV vaccine or placebo.

3.15.8 Analysis of immunogenicity

3.15.8.1 Immunogenicity of the HRV vaccine for the subset planned to receive two doses of HRV vaccine or placebo

GMCs and seropositivity rates to anti-rotavirus IgA antibodies were calculated with their 95% CI for each group, at each time point that blood samples were available. GMCs (expressed in U/ml) were computed by taking the anti-log of the mean of the log titer transformations. Antibody concentrations below the cut-off were given an arbitrary value of half the cut-off for the purpose of GMC calculation.

A subject who had seroconverted for anti-rotavirus IgA antibodies at a post-vaccination sampling timepoint was defined as a subject with appearance of anti-rotavirus IgA antibody concentration ≥ 20 U/ml in subjects initially (i.e. prior to the first dose of HRV vaccine or placebo) negative for RV. The seroconversion rate was the seropositivity rate at the post-vaccination sampling timepoint in subjects initially negative for RV (for the ATP cohort, at post Dose 1 and post Dose 2 time point, seroconversion rate = seropositivity rate).

Seroconversion rate on combined doses was also calculated, using the rule describe below:

Rule for calculating seroconversion on combined doses 1 and 2, at Visit 3:

Seroconversion in the blood sample taken after Dose 2 at Visit 3	Seroconversion in the blood sample taken after Dose 1 (at Visit 2)	Estimate seroconversion rate for the blood sample taken at Visit 3 (i.e., based on the result of column 1 and 2)
Yes	Yes, No or Unknown	Seroconversion
No	Yes	Seroconversion
No	No	No seroconversion
No	Unknown	No seroconversion
Unknown	Yes	Seroconversion
Unknown	No	NC
Unknown	Unknown	NC

NC = Not considered in the calculation

The distribution of anti-rotavirus IgA antibody concentrations at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period were displayed using reverse cumulative curves.

In order to compare antibody concentrations induced by the vaccine across the studies, and also to compare with antibody concentrations induced by natural RV infection, anti-rotavirus IgA antibody GMCs were also calculated on the subjects who had seroconverted after vaccination or natural infection.

Stool analysis subset:

The stool analysis subset consisted of subjects with at least one available result for stools collected at pre-determined timepoints.

GMCs and seropositivity rates to anti-rotavirus IgA antibodies were calculated with their 95% CI for each group, at each time point that blood samples were available. GMCs were computed by taking the anti-log of the mean of the log titer transformations. Antibody concentrations below the cut-off were given an arbitrary value of half the cut-off for the purpose of GMC calculation.

RV shedding was evaluated by calculating the percentage of subjects with presence of RV in stool samples collected at Day 0 and Day 7 of each HRV vaccine or placebo dose and after combined doses.

The percentage of subjects with vaccine take after each HRV vaccine or placebo dose and after combined doses were calculated with their exact 95% CI. Vaccine take rates were defined as the percentage of subjects with appearance of serum anti-rotavirus IgA antibody concentration ≥ 20 U/ml or vaccine virus in any stool sample collected during the specified period in subjects initially negative for rotavirus. In this study, vaccine take was calculated only for the stool analysis subset.

Vaccine take rates were calculated using the rule described below:

Rule for estimating vaccine take after Dose 1:

Seroconversion in the blood sample taken after Dose 1 (at Visit 2)	Vaccine virus in any stools collected from Dose 1 to the blood sample taken at Visit 2	Estimate vaccine take for the blood sample taken at Visit 2 (i.e., based on the result of column 1 and 2)
Yes	Yes, No or Unknown	**Vaccine take**
No	Yes	**Vaccine take**
No	No	No vaccine take
No	Unknown	No vaccine take
Unknown	Yes	**Vaccine take**
Unknown	No	NC
Unknown	Unknown	NC

NC = Not considered in the calculation

Rule for estimating vaccine take after Dose 2:

Seroconversion in the blood sample taken after Dose 2 at Visit 3	Vaccine virus in any stool collected from Dose 2 to the blood sample taken at Visit 3	Estimate vaccine take for the blood sample taken at Visit 3 (i.e., based on the result of column 1 and 2)
Yes	Yes, No or Unknown	**Vaccine take**
No	Yes	**Vaccine take**
No	No	No vaccine take
No	Unknown	No vaccine take
Unknown	Yes	**Vaccine take**
Unknown	No	NC
Unknown	Unknown	NC

NC = Not considered in the calculation

Vaccine take on combined Doses 1 and 2, at Visit 3:

Seroconversion in the blood sample taken after Dose 2 at Visit 3	Vaccine virus in any stool collected from Dose 1 to the blood sample taken at Visit 3 or seroconversion in the blood sample taken after Dose 1 (at Visit 2)	Estimate vaccine take for the blood sample taken at Visit 3 (i.e., based on the result of column 1 and 2)
Yes	Yes, No or Unknown	**Vaccine take**
No	Yes	**Vaccine take**
No	No	No vaccine take
No	Unknown	No vaccine take
Unknown	Yes	**Vaccine take**
Unknown	No	NC
Unknown	Unknown	NC

NC = Not considered in the calculation

Differences between each HRV vaccine group and placebo were evaluated with respect to vaccine take on combined doses at two months after Dose 2 (at Visit 3) by calculating the asymptotic standardized two-sided 95% CI for difference in vaccine take between each HRV vaccine group and the placebo group.

Impact of feeding on immunogenicity of the HRV vaccine

The impact of feeding on the vaccine take at two months after Dose 2 of HRV vaccine or placebo, on combined doses, was explored using a logistic regression. Only the HRV vaccinated subjects were accounted in the regression. A stepwise procedure was used to identify the statistically significant factors among those described below.

Category	Dose
Only breast-fed	at both doses at the first dose only at the second dose only for none of the doses
Breast-fed + formula-fed	at both doses at the first dose only at the second dose only for none of the doses
Fed within 1 hour before vaccination	at both doses at the first dose only at the second dose only for none of the doses
Fed within 30 minutes after vaccination	at both doses at the first dose only at the second dose only for none of the doses
Group	HRV $10^{4.7}$ HRV $10^{5.2}$ HRV $10^{5.8}$

A 2-sided p-value less than 0.10 for the factor effect was used to retain or discard a factor as being not significant.

Vaccine take on combined doses was to be calculated according to the findings of the logistic regression.

3.15.8.2 Immunogenicity of routine DTPw-HBV+Hib and OPV vaccines for the subset receiving two doses of HRV vaccine or placebo

Analysis of immunogenicity of routine vaccinations for the ATP cohort was performed on the subset of subjects who had documented receipt of at least two doses of routine vaccines between Visit 1 and before the end of the first efficacy follow-up period.

The following calculations were done for each study group and for pooled HRV vaccine groups:

GMC/Ts and seropositivity/seroprotection rates for anti-diphtheria, anti-tetanus, anti-BPT, anti-HBs, anti-PRP, anti-poliovirus types 1, 2 and 3 antibodies were calculated with their 95% CI. GMC/Ts were computed by taking the anti-log of the mean of the log titer transformations. Antibody concentrations below the cut-off were given an arbitrary value of half the cut-off for the purpose of GMC/T calculation.

Differences between the pooled HRV vaccine group/each HRV vaccine group and placebo group with respect to immune response to concomitant vaccination at two months after Dose 2 of HRV vaccine or placebo and at the end of first efficacy follow up period were evaluated using:

- asymptotic standardized two-sided 95% CI for the differences in seroprotection or seropositivity rates between groups.
- two-sided 95% CI for the ratio of GMC/Ts between groups. This calculation was performed using a one-way ANOVA model on the logarithm10 transformation of the concentrations using the vaccine group as only covariate.

These inferential analyses were exploratory and clinical limits for non-inferiority were not pre-defined.

The distribution of antibody concentrations/titers two months after Dose 2 of HRV or placebo and at the end of the first efficacy follow-up period were displayed using reverse cumulative curves.

3.15.8.3 Immunogenicity analysis for the subset receiving three doses of HRV vaccine or placebo

At each time point that antibodies to a given antigen (HRV or placebo, DTPw-HB+Hib and OPV) were measured, GMC/Ts and seroconversion/seroprotection/seropositivity rates were calculated with their 95% CI for each group.

The distribution of anti-rotavirus IgA antibody concentrations at two months after Dose 2 of HRV vaccine or placebo and at two months after Dose 3 of HRV vaccine or placebo were displayed using reverse cumulative curves.

Anti-rotavirus IgA antibody GMCs were also calculated on the subjects who had seroconverted after vaccination or natural infection.

RV shedding was evaluated by calculating the percentage of subjects with presence of RV in stool samples collected at pre-determined timepoints after vaccination.

The distribution of antibody levels induced by routine vaccinations at two months after Dose 3 of HRV vaccine or placebo were displayed using reverse cumulative curves.

3.16 Interim analyses

Five interim analyses were performed as planned in the protocol. Unblinding and access to the individual treatment code during each interim analysis was restricted to the statistician and the database administrator. No study report was written for the interim analyses and dissemination of results of the interim analyses was strictly controlled. The results of all the interim analyses mentioned below are available ([9]).

- In March 2002, a planned interim analysis was performed to provide early information for dose selection. This analysis presented a descriptive summary of immunogenicity and reactogenicity for the study vaccine and immunogenicity data for routine vaccinations. The results of this interim analysis were consistent with the results presented in this study report.

- In August 2002, a planned interim analysis on efficacy against any and severe RV GE, overall and by type was performed to obtain preliminary efficacy data. This interim efficacy analysis was performed when the number of RV GE cases from two weeks after Dose 2 of HRV vaccine or placebo reached 70. This allowed demonstration of efficacy (with LL of 95% CI >0) with 75% power based on the following conservative assumption: vaccine efficacy (for pooled HRV vaccine groups) against any RV GE is 50%, with an attack rate of 6% in the placebo group. No adjustment on the alpha or the power were applied for the final analyses of efficacy. The results of this interim analysis were consistent with the results presented in this study report.

- In February 2003, a planned interim analysis on data after Dose 3 of HRV vaccine or placebo was performed. This analysis presented a descriptive summary of immunogenicity for the study vaccines. The results of this interim analysis were consistent with the results presented in this study report.

- In September 2003, analyses for transplacental anti-rotavirus IgG antibodies and transplacental anti-rotavirus neutralizing antibodies in study rota-008 (annex protocol implemented in a subset from study rota-006) were performed. The results of the analyses are presented in the report "The Interference of Transplacental Antibodies on Response to GSK Biologicals' Human Rotavirus Vaccine: Rota-004, Rota-008 and Rota-014".

- In October 2003, a planned interim analysis on efficacy against any and severe RV GE at the end of the second efficacy follow-up period in Mexico was performed to obtain early efficacy data during the second efficacy follow-up period. No adjustment on the alpha or the power will be applied for the final analyses of efficacy. A separate annex report will present efficacy and safety data during the second efficacy follow-up period from all subjects (from Brazil, Mexico and Venezuela) who were followed until maximum age 24 months.

The results of interim analyses were presented at scientific conferences and to the authorities, as required, however unblinding at the level of individual data was restricted to the statistician and the database administrator.

3.17 Annex analyses

A separate annex report will present efficacy and safety data during the second efficacy follow-up period as well as efficacy over two consecutive follow-up periods from all subjects who were followed until maximum age 24 months.

A separate report will present all data obtained during study rota-008.

A separate report will present all data on characterisation of the immune response of the HRV vaccine (maternal antibodies and neutralizing antibodies) from subsets of subjects enrolled in study rota-006.

A separate report will present all data obtained during the site-specific evaluation of fecal RV IgA immune response in a subset of subjects enrolled in study rota-006 in Venezuela.

3.18 Changes in conduct of the study/planned analyses

The following changes were made to the planned analyses:

- The total vaccinated cohort was used for the analyses instead of the total cohort.
- If RV was detected in stool samples collected at pre-determined timepoints from subjects in the placebo group, G type was determined *post-priori* by RT-PCR at GSK Biologicals, Rixensart, Belgium.
- An increase in the incidence of specific symptoms after vaccine administration (pooled HRV vaccine groups) as compared to placebo, was explored using a two-sided Fisher's exact test (with an alpha of 5%) instead of a one-sided Fisher's exact test (with an alpha of 5%) to standardize with future studies.

- The standardized asymptotic method was used for inference on the difference of two proportions instead of exact method by Santner and Snell specified in the protocol. The type 1 error and the power were not impaired due to this change.
- Vaccine efficacy estimates against pure and mixed RV GE was not calculated since no concurrent pathogen was identified in the majority of RV GE episodes.
- Since none of the assessed factors (feeding criteria) had a significant effect in the logistic regression, the vaccine take by feeding criteria were not calculated.
- For the subjects receiving three doses of HRV vaccine or placebo, serum levels of antibodies to routine vaccinations were measured also at two months after Dose 2 of HRV vaccine or placebo, although not planned in the protocol.

4 Study population planned to receive two doses of HRV vaccine or placebo

4.1 Study dates

The study began on May 25, 2001 (first subject, first visit). The data lock point for this final analysis was April 24, 2003 (the day on which the last subject completed the study visit at the end of the first efficacy follow-up period).

A subset of approximately 1000 subjects was followed for efficacy during the second efficacy follow-up period (until maximum age 24 months). The second efficacy follow-up period in Mexico ended in June 2003 (after the end of the 2003 RV season). The second efficacy follow-up period in Brazil and Venezuela ended in October 2003.

4.2 Subject eligibility and attrition from study

4.2.1 Number and distribution of subjects

A total of 2155 subjects were enrolled in the study to receive two doses of HRV vaccine or placebo after checking of inclusion/exclusion criteria. The number of subjects at each study centre is presented in Table 10.

Table 10: The number of subjects enrolled at each study centre by group (total vaccinated cohort)

Country	Centre	Group					
		HRV $10^{4.7}$	HRV $10^{5.2}$	HRV $10^{5.8}$	Placebo	All	
		n	n	n	n	n	%
Brazil	[redacted]	194	196	194	194	778	36.1
Mexico	[redacted]	101	101	102	101	405	18.8
Venezuela	[redacted]	243	243	244	242	972	45.1
All	All	538	540	540	537	2155	100

Notes: Centre = GSK assigned centre number
n = number of subjects enrolled in each group or in total for a given centre or for all centres
% = percentage of subjects enrolled for a given centre or for all centres
All = sum of all subjects in each group, in total for all groups or in total for all centres

4.2.2 Study completion and drop out

A total of 151 subjects dropped out of the study until the end of the first efficacy follow-up period for reasons detailed in Table 11.

Table 11: Counts of subjects enrolled, completed, dropped out and reason for drop out until the end of the first efficacy follow-up period (total vaccinated cohort)

	Groups				Total
	HRV $10^{4.7}$	HRV $10^{5.2}$	HRV $10^{5.8}$	Placebo	
Number of subjects enrolled	538	540	540	537	2155
Number of subjects completed	500	499	499	506	2004
Number of subjects dropped out	38	41	41	31	151
Reasons for drop-out:					
SAE	1	0	1	1	3
Non-serious AE	0	2	2	2	6
Protocol violation	0	0	1	1	2
Consent withdrawal (not due to an adverse event)	13	21	9	9	52
Migrated/moved from study area	21	17	24	18	80
Lost to follow-up (subjects with incomplete vaccination course)	1	0	1	0	2
Lost to follow-up (subjects with complete vaccination course)	1	0	0	0	1
Others	1	1	3	0	5

Notes: Enrolled = number of subjects who were enrolled in the study
Completed = number of subjects who completed Visit 4 at the end of the first efficacy follow-up period
Dropped out = number of subjects who did not come at Visit 4 at the end of the first efficacy follow-up period

Most of the subjects dropped either because of consent withdrawal or because they moved from the study area.

Three subjects died due to unrelated SAEs. Refer to Section 6.2.6.2 for details on SAEs with a fatal outcome.

Details of the non-serious adverse events that led to six drop outs are as follows:

Drop outs due to non-serious AEs assessed as related to vaccination:

- One subject was withdrawn after Dose 1 of HRV vaccine or placebo after experiencing an allergic reaction (grade 2 intensity) starting on the day of Dose 1. The subject recovered after two weeks. The subject had received DTPw-HB+Hib vaccine concomitantly with the study vaccine. It was not specified whether the study vaccine or the routine concomitant vaccine caused the allergic reaction.

Drop outs due to non-serious AEs assessed as not related to vaccination:

- One subject had a history of gastrointestinal reflux that was recorded by the study physician when Dose 1 of HRV vaccine or placebo was administered. The subject received Dose 2 of HRV vaccine or placebo. Thereafter, the intensity of the gastrointestinal reflux changed from moderate to severe and the subject did not return for the study visit at the end of the first efficacy follow-up period. The AE was still ongoing at the last contact.

- One subject dropped out post Dose 2 of HRV vaccine or placebo after developing severe anaemia (grade 3 intensity) starting 254 days after Dose 2. The outcome of this event is not known.

- Subject dropped out post Dose 1 of HRV vaccine or placebo due to events following reaction to BCG vaccination (grade 3 intensity). The subject had received BCG vaccine 56 days before the first dose of HRV vaccine or placebo. The physician evaluating the subject prescribed antibiotics for a period of at least 6 months and asked for examination every 15 days. Due to these events the subject was withdrawn by the clinical study staff.

- One subject dropped out post Dose 2 of HRV vaccine or placebo after developing hypothyroidism (grade 1 intensity) starting on Day 108 after Dose 2. The AE was still ongoing at the last contact.

- One subject dropped out post Dose 1 of HRV vaccine or placebo after developing cervical lymphangioma (grade 2 intensity) starting on Day 117 after Dose 1. The AE was still ongoing at the last contact.

Two subjects dropped out with the reason stated as "protocol violation": one did not return for Visit 2 (received Dose 2 routine vaccines outside of the study) and one did not return for Visit 4 at the end of the first efficacy follow-up period.

Five subjects dropped out following advice from their family doctor. The reason for drop out was classified as "other" for these subjects.

4.2.3 Eligibility for analysis

Reasons for elimination from the ATP analyses are summarized in Table 12. See *Appendix A: Clintrial eligibility codes* for definitions of codes.

Table 12: Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses with reasons for exclusion

Title	Total	%	HRV $10^{4.7}$	HRV $10^{5.2}$	HRV $10^{5.8}$	Placebo
Number of vaccines prepared	**2759**		**689**	**690**	**690**	**690**
Subjects or vaccine number not allocated (code 1010)	604		151	150	150	153
Total enrolled cohort	**2155**		**538**	**540**	**540**	**537**
Total vaccinated cohort	**2155**	**100**	**538**	**540**	**540**	**537**
Administration of vaccine(s) forbidden in the protocol (code 1040)	38		10	11	8	9
Randomisation failure (code 1050)	4		0	1	2	1
Randomisation code broken at the investigator site (code 1060)	1		0	0	0	1
Study vaccine dose not administered according to protocol (code 1070)	96		20	27	19	30
Initially positive or unknown status for rotavirus on the day of Dose 1 (code 1500)	51		9	14	18	10
ATP cohort for safety analysis	**1965**	**91.2**	**499**	**487**	**493**	**486**
➢ Administration of any medication forbidden by the protocol (code 2040)	101		22	27	24	28
Concomitant infection by rotavirus other than vaccine strain which may influence immune response (code 2060)	45		7	8	5	25
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	88		18	21	26	23
Non compliance with blood sampling schedule (including wrong and unknown date) (code 2090)	58		19	9	15	15
Essential serological data missing (code 2100)	147		38	45	42	22
ATP cohort for immunogenicity analysis	**1526**	**70.8**	**395**	**377**	**381**	**373**
➢ At least one study vaccine dose not administered (code 3010)	80		21	26	22	11
Subjects not entered into the surveillance period of the first efficacy follow-up period (code 3020)	10		3	0	3	4
Concomitant infection by rotavirus other than vaccine strain up to 2 weeks after dose 2 which may influence efficacy response (code 3030)	29		7	1	4	17
ATP cohort for efficacy analysis for the first efficacy follow-up period	**1846**	**85.7**	**468**	**460**	**464**	**454**

Notes: % = percentage of subjects in the considered ATP cohort relative to the total vaccinated cohort
Comments: Subjects may have one or more elimination code(s) assigned for exclusion from a specific cohort. In that case the lowest code number is listed in the figure.
The ATP cohort for safety analysis includes all vaccinated subjects with no elimination codes beginning with one thousand. The ATP cohort for immunogenicity analysis includes all vaccinated subjects with no elimination codes beginning with one or two thousand. The ATP cohort for efficacy analysis during the first efficacy follow-up period includes all vaccinated subjects with no elimination codes beginning with one or three thousand.

ATP cohort for safety analysis

Of the 2155 subjects who were enrolled to receive two doses of HRV vaccine or placebo, 190 subjects were eliminated from ATP cohort for safety analysis for the following reasons:

- Thirty-eight subjects received vaccinations forbidden by the protocol (either OPV within 2 weeks of HRV vaccine or placebo dose or BCG/yellow fever vaccinations during the study).
- Randomization failed for four subjects: One subject received Dose 1 and Dose 2 of HRV vaccine or placebo assigned to him and one additional dose of study vaccine that was actually assigned to another subject. Three subjects received a wrong replacement vial.
- The randomization code was broken for one subject who had a SAE (death due to generalized visceral congestion). Refer to Section 6.2.6.2 for details of this case.
- Ninety-six subjects regurgitated within 30 minutes after oral administration of the HRV vaccine or placebo and may not have received the intended study vaccine dose.
- Fifty-one subjects were initially positive for RV or their RV status was unknown on the day of Dose 1 of HRV vaccine or placebo.

Thus, 1965 subjects were included in the ATP cohort for safety analysis.

ATP cohort for immunogenicity analysis

Of the 1965 subjects included in the ATP cohort for safety analysis, 439 subjects were eliminated from the ATP cohort for immunogenicity analysis for the following reasons:

- A total of 101 subjects were eliminated because they had received a medication forbidden by the protocol.
- GE stool samples collected between Visit 1 to Visit 3 from 45 subjects were positive for RV other than the vaccine strain.
- Eighty-eight subjects were eliminated due to non-compliance with vaccination schedule since they received Dose 2 of HRV vaccine or placebo outside of the interval of 49–83 days between vaccinations.
- Fifty-eight subjects were eliminated due to non-compliance with blood sampling schedule.

- A total of 147 subjects were eliminated because of essential immunogenicity (serum or stool analysis) data missing.

Thus, 1526 subjects were included in the ATP cohort for immunogenicity analysis.

ATP cohort for efficacy analysis
Of the 1965 subjects included in the ATP cohort for safety analysis, 119 subjects were eliminated from the ATP cohort for efficacy analysis for the first efficacy follow-up period for the following reasons:

- Eighty subjects did not receive the second dose of HRV vaccine or placebo.
- Ten subjects dropped out before the start of the first efficacy follow-up period.
- GE stool samples collected between Visit 1 to Visit 2 from 29 subjects were positive for RV other than the vaccine strain

Thus, 1846 subjects were included in the ATP cohort for efficacy analysis.

The number of subjects in the respective total vaccinated cohorts (efficacy, immunogenicity and safety) were determined based on the definition of cohorts in Section 3.15.4.

4.2.4 Compliance with protocol specified procedures

Written informed consent was obtained from parents/guardians of all subjects prior to entry in the study.

A total of 2004 of the 2155 enrolled subjects completed the study visit at the end of the first efficacy follow-up period. Therefore compliance with study completion until the end of the first efficacy follow-up period was 93%. Refer to Section 4.2.2 for further information.

Deviations from protocol-specified procedures that were considered as clinically relevant resulted in elimination of the subjects from analyses. Refer to Section 4.2.3 for further information.

The number of doses given and the number of completed symptom sheets (see definition in glossary of terms) for solicited symptoms, as well as the number of doses that were not given according to protocol for the total vaccinated cohort are detailed in Supplement 1. Symptom sheets were completed for the majority (> 97%) of doses in each group indicating high compliance for reactogenicity reporting. There were only few missing reactogenicity data indicating that symptom sheets were properly completed and this is an indication of good quality data. Subjects who regurgitated within 30 minutes and thus did not receive the dose according to the protocol were eliminated from ATP analyses (Refer to Section 4.2.3).

Subjects who did not respect the protocol-specified intervals between vaccinations or for blood sampling at Visit 2 and 3 were eliminated from the ATP cohort for immunogenicity analysis for subjects planned to receive two doses of HRV vaccine or placebo. Refer to Section 4.2.3. Supplement 2 presents deviations from specifications for age and intervals between visits stated in the study protocol.

For the ATP efficacy cohort, ELISA results for stool samples collected during GE episodes in the first efficacy follow-up period were not available for 23.1% episodes in the $10^{4.7}$ ffu HRV vaccine group, 28.3% episodes in the $10^{5.2}$ ffu HRV vaccine group, 29.8% episodes in the $10^{5.8}$ ffu HRV vaccine group and 22.7% episodes in the placebo group. Results were unavailable due to stool samples not collected during GE episodes or RV ELISA test not performed or an invalid result. See Supplement 3.

Weekly visits to the subjects' home by the Health Care workers were planned for GE surveillance. However, this activity was not to be documented and therefore compliance cannot be assessed.

Compliance for administration of routine DTPw-HB+Hib vaccine in the subset planned to receive two doses of HRV vaccine or placebo was as follows:

- In the total vaccinated cohort, more than 98% of subjects in each group received the DTPw-HB+Hib vaccine concomitantly with Dose 1 and Dose 2 of HRV vaccine or placebo.

- In the ATP cohort for immunogenicity, more than 98% of subjects in each group received the DTPw-HB+Hib vaccine concomitantly with Dose 1 and Dose 2 of HRV vaccine or placebo. None of the subjects received OPV concomitantly with Dose 1 and Dose 2 of HRV vaccine or placebo.

- In the ATP cohort for immunogenicity for subjects with available routine vaccination serology results at Visit 3, more than 93% of subjects in each group

received two doses of DTPw-HB+Hib and OPV vaccines between Visit 1 and before Visit 3.

- In the ATP cohort for immunogenicity for subjects with available routine vaccination serology results at the end of the first efficacy follow-up period, more than 94% of subjects in each group received three doses of DTPw-HB+Hib and OPV vaccines between Visit 1 and before the end of the first efficacy follow-up period.

4.3 Demographic characteristics

4.3.1 Total vaccinated cohort

Demographic characteristics for the total vaccinated cohort are summarized in Supplement 4. The mean age at the time of Dose 1 of HRV vaccine or placebo was 8.3 weeks (range 6–12 weeks). The mean age at the time of Dose 2 of HRV vaccine or placebo was 17.9 weeks (range 13–28 weeks). The demographic profile of the four groups was similar with respect to mean age, mean height and mean weight at the time of Dose 1 of HRV vaccine or placebo and race distribution. Observed differences in female to male ratio between the groups can be attributed to random chance and are not deemed clinically relevant.

Demographic characteristics by country are summarized in Supplement 5, Supplement 6 and Supplement 7. The demographic characteristics of the cohort differed between the countries for some aspects (e.g. mean age at Dose 1 of HRV vaccine or placebo and race distribution). However, for each given country, the demographic profile was similar between the four groups.

Supplement 8 presents the weight and height increases from Visit 1 to each of the subsequent visits until the end of the first efficacy follow-up period by group. The mean increase in height and weight from Visit 1 to Visits 2, 3 and 4 was similar among the four groups.

4.3.2 Subjects included in the ATP cohort for efficacy analysis

Demographic characteristics for the ATP cohort for efficacy analysis are summarized in Table 13. The demographic characteristics for the ATP cohort for efficacy analysis were similar to the demographic characteristics for the total vaccinated cohort.

Table 13: Summary of demographic characteristics (ATP cohort for efficacy analysis)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N = 468		HRV $10^{5.2}$ N = 460		HRV $10^{5.8}$ N = 464		Placebo N = 454		Total N = 1846	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age at first dose (weeks)	Mean	8.3	-	8.4	-	8.3	-	8.4	-	8.3	-
	SD	1.51	-	1.47	-	1.50	-	1.55	-	1.50	-
	Median	8	-	8	-	8	-	8	-	8	-
	Minimum	6	-	6	-	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	215	45.9	232	50.4	212	45.7	227	50.0	886	48.0
	Male	253	54.1	228	49.6	252	54.3	227	50.0	960	52.0
Race	Black	19	4.1	12	2.6	15	3.2	11	2.4	57	3.1
	White/Caucasian	98	20.9	116	25.2	124	26.7	111	24.4	449	24.3
	Oriental	0	0.0	0	0.0	0	0.0	1	0.2	1	0.1
	Other	351	75.0	332	72.2	325	70.0	331	72.9	1339	72.5
Height (cm)	Mean	57.4	-	57.5	-	57.5	-	57.6	-	57.5	-
	SD	2.75	-	2.59	-	2.90	-	2.92	-	2.80	-
	Median	57	-	58	-	57	-	58	-	57	-
	Unknown	2	-	1	-	1	-	1	-	5	-
Weight (kg)	Mean	5.3	-	5.3	-	5.3	-	5.3	-	5.3	-
	SD	0.75	-	0.67	-	0.74	-	0.76	-	0.70	-
	Median	5.2	-	5.3	-	5.3	-	5.3	-	5.3	-
	Unknown	2	-	0	-	1	-	1	-	4	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

4.3.3 Subjects included in the ATP cohort for immunogenicity analysis

Demographic characteristics for the subjects included in the ATP cohort for immunogenicity analysis are summarized in Supplement 9. The demographic characteristics for the ATP cohort for immunogenicity analysis were similar to the demographic characteristics for the total vaccinated cohort.

Supplement 10 presents the percentage of subjects who received OPV at birth. The proportion of subjects who received OPV at birth was similar for the four groups and ranged between 11.8% to 16.2%.

Supplement 11 presents a summary of feeding criteria on the day of each study vaccination by group. The feeding profile (percentage of subjects who were fed with breast milk, infant formula or both) of the four groups was similar. Most subjects were fed with breast milk or received both breast milk and infant formula. The percentage of subjects fed with breast milk decreased from Dose 1 to Dose 2 of HRV vaccine or placebo.

5 Analysis of efficacy in subjects planned to receive two doses of HRV vaccine or placebo

5.1 Data sets analyzed

Analysis of efficacy was performed on the ATP cohort (primary analysis) and the total vaccinated cohort. See Section 3.15.4 for definition of cohorts identified for analyses and Section 4.2.3 for description of eligibility for analyses.

5.2 ATP analysis

The ATP cohort for efficacy analysis consisted of 1846 subjects (468 subjects in the $10^{4.7}$ ffu HRV vaccine group, 460 subjects in the $10^{5.2}$ ffu HRV vaccine group, 464 subjects in the $10^{5.8}$ ffu HRV vaccine group and 454 subjects in the placebo group).

5.2.1 Characterization of GE episodes reported during the first efficacy follow-up period

The first efficacy follow-up period started from two weeks after Dose 2 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age).

The duration of follow-up was similar for the four groups, with a mean duration of 7 months. Refer to Supplement 12 for duration of follow-up for the first efficacy period.

Table 14 presents a summary of intensity of GE episodes of any etiology (RV or not) and RV GE episodes reported during the first efficacy follow-up period. Supplement 13 presents the percentage of subjects who reported GE episodes of any etiology (RV or not) and RV GE episodes during the first efficacy follow-up period.

During the first efficacy follow-up period, 411 GE episodes were reported for 197 subjects in the $10^{4.7}$ ffu HRV vaccine group, 385 GE episodes for 181 subjects in the $10^{5.2}$ ffu HRV vaccine group, 420 GE episodes for 195 subjects in the $10^{5.8}$ ffu HRV vaccine group and 419 GE episodes for 214 subjects in the placebo group (See Table 14 and Supplement 13). As seen from Supplement 13, the percentages of subjects who reported GE episodes of any etiology (RV or not) during the first efficacy follow-up period was similar between the groups: 42.1% in the $10^{4.7}$ ffu HRV vaccine group, 39.3% in the $10^{5.2}$ ffu HRV vaccine group, 42.0% in the $10^{5.8}$ ffu HRV vaccine group and 47.1% in the placebo group.

As seen from Table 14, a total of 109 RV GE episodes were reported during the first efficacy follow-up period. As seen from Supplement 13, the percentage of subjects reporting RV GE was lower in the three HRV vaccine groups (4.5% in the $10^{4.7}$ ffu HRV vaccine group, 4.8% in the $10^{5.2}$ ffu HRV vaccine group and 3.2% in the $10^{5.8}$ ffu HRV vaccine group) as compared to the placebo group (10.8%).

As seen from Supplement 13, no subject in the HRV vaccine groups had more than one episode of RV GE while two subjects from the placebo group had two episodes of RV GE (one subject had two episodes attributed to G1 wild-type RV while the other subject had one episode attributed to G9 type and one episode attributed to the G1 wild-type RV).

As seen from Table 14, 57.1% of RV GE episodes in the $10^{4.7}$ ffu HRV vaccine group, 45.5% of RV GE episodes in the $10^{5.2}$ ffu HRV vaccine group, 33.3% of RV GE episodes in the $10^{5.8}$ ffu HRV vaccine group and 66.7% of RV GE episodes in the placebo group were noted as severe (a score ≥ 11 on a 20-point scale).

Table 14: Number of GE episodes and RV GE episodes reported during the first efficacy follow-up period, by severity (ATP cohort for efficacy analysis)

		HRV $10^{4.7}$		**HRV $10^{5.2}$**		**HRV $10^{5.8}$**		**Placebo**	
Event	**Severity**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
GE of any etiology (RV or not)	**Mild (1-6)**	190	46.2	202	52.5	214	51.0	185	44.2
	Moderate (7-10)	127	30.9	114	29.6	132	31.4	123	29.4
	Severe (≥11)	94	22.9	69	17.9	74	17.6	111	26.5
	Any	411	100	385	100	420	100	419	100
RV GE	**Mild (1-6)**	4	19.0	8	36.4	2	13.3	5	9.8
	Moderate (7-10)	5	23.8	4	18.2	8	53.3	12	23.5
	Severe (≥11)	12	57.1	10	45.5	5	33.3	34	66.7
	Any	21	100	22	100	15	100	51	100

Notes: n/% = number/percentage of GE or RV GE episodes reported in each group, by severity, among all GE or RV GE episodes reported in the first efficacy follow-up period
Any = any specified symptom, regardless of severity

Stool analysis results were not available for 26% of the reported GE cases due to stool samples not collected during GE episodes or RV ELISA test not performed or invalid result. Refer to Section 4.2.4.

Table 15 presents the percentage of subjects reporting RV GE episodes during the first efficacy follow-up period by RV G type.

The predominant RV types during the first efficacy follow-up period were wild-type G1 (identified in 50.5% of RV GE episodes) and G9 (identified in 39.4% of RV GE episodes). In addition, G2, G3 and G4 types were also isolated during the first efficacy follow-up period. RV G type could not be identified for two subjects in the $10^{5.2}$ ffu HRV vaccine group.

Table 15: Percentage of subjects with RV GE episodes reported during the first efficacy follow-up period, by RV G type (ATP cohort for efficacy analysis)

Type	HRV $10^{4.7}$ N = 468		HRV $10^{5.2}$ N = 460		HRV $10^{5.8}$ N = 464		Placebo N = 454	
	n	%	n	%	n	%	n	%
Any	21	4.5	22	4.8	15	3.2	49	10.8
G1 wild type	12	2.6	6	1.3	7	1.5	29	6.4
G2	0	0.0	0	0.0	1	0.2	3	0.7
G3	1	0.2	0	0.0	0	0.0	2	0.4
G4	0	0.0	0	0.0	1	0.2	0	0.0
G9	8	1.7	14	3.0	7	1.5	15	3.3
Canine	0	0.0	0	0.0	0	0.0	1	0.2
Unknown	0	0.0	2	0.4	0	0.0	0	0.0

Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified type in each group
Any = RV GE episode, whatever the type

Supplement 14 presents the characteristics of GE episodes reported during the first efficacy follow-up period. The rate of hospitalization was lower in the HRV vaccine groups as compared to the placebo group while other characteristics of GE episodes were similar between the groups.

Supplement 15 presents the characteristics of RV GE episodes reported during the first efficacy follow-up period. As seen from Supplement 15, the duration of vomiting and diarrhea, level of dehydration and rate of hospitalization for any RV GE episodes were lower in the HRV vaccine groups as compared to the placebo group. Supplement 16 and Supplement 17 respectively present the characteristics of RV GE episodes caused by G1 wild-type and G9 type reported during the first efficacy follow-up period.

Supplement 18 presents the percentage of RV GE episodes with mixed infections during the first efficacy follow-up period. No concurrent pathogen was identified in the majority (94.5%) of RV GE episodes. Only six mixed RV GE episodes were reported (one in the $10^{4.7}$ ffu HRV vaccine group, two in the $10^{5.8}$ ffu HRV vaccine group and three in the placebo group).

Supplement 19 presents the percentage of subjects in the HRV vaccine groups reporting RV GE according to the serological status of anti-rotavirus IgA antibodies at two months after Dose 2 of HRV vaccine or placebo.

5.2.2 Vaccine efficacy against RV GE during the first efficacy follow-up period

Table 16 presents the efficacy of the HRV vaccine against RV GE of any intensity during the first efficacy follow-up period. Table 17 presents the efficacy of the vaccine against severe RV GE during the first efficacy follow-up period.

There was a statistically significant decrease in the percentage of subjects reporting any RV GE and severe RV GE during the first efficacy follow-up period in pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group (p-value < 0.001, two-sided Fisher's exact test). The primary objective (efficacy against any RV GE from 2 weeks after Dose 2 of HRV vaccine or placebo until the end of the efficacy follow-up period) of the study was reached.

There was a trend towards increased efficacy against any and severe RV GE in the $10^{5.8}$ ffu HRV vaccine group *versus* other HRV vaccine groups.

Table 16: Percentage of subjects reporting any RV GE and efficacy of the vaccine during the first efficacy follow-up period (ATP cohort for efficacy analysis)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**p-value**
HRV $10^{4.7}$	468	21	276.4	0.076	0.050	0.117	4.5	2.8	6.8	58.4	29.4	76.3	<0.001
HRV $10^{5.2}$	460	22	268.4	0.082	0.054	0.124	4.8	3.0	7.2	55.7	25.3	74.5	<0.001
HRV $10^{5.8}$	464	15	272.2	0.055	0.033	0.091	3.2	1.8	5.3	70.0	45.7	84.4	<0.001
Pooled HRV Groups	1392	58	817.0	0.071	0.055	0.092	4.2	3.2	5.4	61.4	42.3	74.1	<0.001
Placebo	454	49	256.5	0.191	0.144	0.253	10.8	8.1	14.0	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one RV GE episode in each group
n/T = person-year rate of RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Table 17: Percentage of subjects reporting severe RV GE and efficacy of the vaccine during the first efficacy follow-up period (ATP cohort for efficacy analysis)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**p-value**
HRV $10^{4.7}$	468	12	279.7	0.043	0.024	0.076	2.6	1.3	4.4	65.8	32.2	83.9	<0.001
HRV $10^{5.2}$	460	10	273.1	0.037	0.020	0.068	2.2	1.0	4.0	71.0	39.9	87.2	<0.001
HRV $10^{5.8}$	464	5	276.1	0.018	0.008	0.044	1.1	0.4	2.5	85.6	63.0	95.6	<0.001
Pooled HRV Groups	1392	27	828.9	0.033	0.022	0.047	1.9	1.3	2.8	74.1	55.8	85.0	<0.001
Placebo	454	34	261.7	0.130	0.093	0.182	7.5	5.2	10.3	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Vaccine efficacy rates against the primary endpoint (occurrence of any RV GE from 2 weeks after Dose 2 of HRV vaccine or placebo until the end of the efficacy follow-up period) estimated by the Cox proportional-hazard model were similar to vaccine efficacy estimates presented in this section.

Supplement 20 presents vaccine efficacy against any RV GE during the first efficacy follow-up period by G type.

- There was a statistically significant decrease in the percentage of subjects reporting any RV GE caused by G1 wild-type during the first efficacy follow-up period in pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test).

- There was a statistically significant decrease in the percentage of subjects reporting any RV GE caused by non-G1 types (either G2, G3, G4 or G9 type) during the first efficacy follow-up period in pooled HRV vaccine groups, in $10^{4.7}$ ffu HRV vaccine group and in $10^{5.8}$ ffu HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test). The percentage of subjects reporting any RV GE caused by non-G1 types was lower, although not statistically significant, in the $10^{5.2}$ ffu HRV vaccine group as compared to the placebo group.

- The percentage of subjects reporting any RV GE caused by G9 type during the first efficacy follow-up period was lower in pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group, but the difference did not reach statistical significance (p-value > 0.05, two-sided Fisher's exact test).

Supplement 21 presents the efficacy of the vaccine against severe RV GE during the first efficacy follow-up period by G type.

- There was a statistically significant decrease in the percentage of subjects reporting severe RV GE caused by G1 wild-type during the first efficacy follow-up period in pooled HRV vaccine groups, in $10^{5.2}$ ffu HRV vaccine group, $10^{5.8}$ ffu HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test). The percentage of subjects reporting severe RV GE caused by G1 wild-type was lower in the $10^{4.7}$ ffu HRV vaccine group as compared to the placebo group, but the difference did not reach statistical significance (p-value > 0.05, two-sided Fisher's exact test).

- There was a statistically significant decrease in the percentage of subjects reporting severe RV GE caused by non-G1 types (either G2, G3, G4 or G9 type) during the first efficacy follow-up period in pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test).

- There was a statistically significant decrease in the percentage of subjects reporting severe RV GE caused by G9 type during the first efficacy follow-up period in pooled HRV vaccine groups, in $10^{4.7}$ ffu HRV vaccine group and in $10^{5.8}$ ffu HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test). The percentage of subjects reporting severe RV GE caused by G9 type was lower, although not statistically significant, in the $10^{5.2}$ ffu HRV vaccine group as compared to the placebo group.

Supplement 22 and Supplement 23 respectively present vaccine efficacy against any and severe RV GE during the first efficacy follow-up period by country.

The vaccine efficacy against any and severe RV GE was lower in Brazil when compared to Mexico and Venezuela. There was a statistically significant decrease in the percentage of subjects reporting any and severe RV GE in pooled HRV vaccine groups in each country as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test).

In each country, there was a statistically significant decrease in the percentage of subjects reporting any RV GE in all HRV vaccine groups as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test), except for $10^{4.7}$ and $10^{5.2}$ ffu HRV vaccine groups in Brazil.

In each country, there was a statistically significant decrease in the percentage of subjects reporting severe RV GE in each HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test), except for $10^{4.7}$ ffu HRV vaccine group in Mexico and Venezuela.

Since no concurrent pathogen was identified in the majority (94.5%) of RV GE episodes, vaccine efficacy against pure and mixed RV GE during the first efficacy follow-up period was not evaluated.

5.2.3 Vaccine efficacy against hospitalization due to RV GE during the first efficacy follow-up period

Table 18 presents the efficacy against hospitalization due to RV GE during the first efficacy follow-up period.

There was a statistically significant decrease in the percentage of subjects hospitalized due to RV GE during the first efficacy follow-up period in pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test).

Table 18: Percentage of subjects hospitalized due to RV GE and efficacy of the vaccine during the first efficacy follow-up period (ATP cohort for efficacy analysis)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**p-value**
HRV $10^{4.7}$	468	5	281.4	0.018	0.007	0.043	1.1	0.3	2.5	65.4	-1.8	90.2	0.037
HRV $10^{5.2}$	460	1	276.1	0.004	0.001	0.026	0.2	0.0	1.2	93.0	53.7	99.8	<0.001
HRV $10^{5.8}$	464	3	276.8	0.011	0.003	0.034	0.6	0.1	1.9	79.0	24.9	96.1	0.007
Pooled HRV Groups	1392	9	834.3	0.011	0.006	0.021	0.6	0.3	1.2	79.0	48.0	92.0	<0.001
Placebo	454	14	267.7	0.052	0.031	0.088	3.1	1.7	5.1	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects hospitalized due to RV GE in each group
T= sum of follow-up period expressed in year censored at the first occurrence of hospitalization due to RV GE episode in the first efficacy follow-up period, in each group
n/N= percentage of subjects hospitalized due to RV GE in each group
n/T= person-year rate of hospitalization due to RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

5.2.4 Total vaccinated cohort for efficacy analysis

The total vaccinated cohort for analysis of efficacy during the first efficacy follow-up period consisted of 2044 subjects (507 subjects in the $10^{4.7}$ ffu HRV vaccine group, 508 subjects in the $10^{5.2}$ ffu HRV vaccine group, 512 subjects in the $10^{5.8}$ ffu HRV vaccine group and 517 subjects the placebo group).

Efficacy data during the first efficacy follow-up period for the total vaccinated cohort are presented in Supplement 24 to Supplement 39.

The results of the total vaccinated cohort analyses were consistent with those observed in the ATP cohort.

5.2.4.1 Vaccine efficacy against RV GE occurring from Dose 1 onwards

In order to have a first look at the effectiviness of the vaccine from the first dose onwards, occurrence of RV GE episodes from Day of Dose1 till Day 14 of Dose 2 and occurrence of RV GE episodes from Day of Dose1 till the end of the first efficacy follow-up period were evaluated.

The total vaccinated cohort for analysis of RV GE occurring from day of Dose 1 onwards consisted of 2155 subjects (538 subjects in the $10^{4.7}$ ffu HRV vaccine group, 540 subjects in the $10^{5.2}$ ffu HRV vaccine group, 540 subjects in the $10^{5.8}$ ffu HRV vaccine group and 537 subjects the placebo group).

Occurrence of RV GE from day of Dose 1 till Day 14 after Dose 2 of HRV vaccine or placebo

Supplement 40 presents the percentage of subjects in each group who reported any or severe RV GE episode(s) from day of Dose 1 till Day 14 after Dose 2. Supplement 40 includes all RV GE episodes caused by wild-type and vaccine strain RV. The percentages of subjects reporting RV GE tended to be lower in the pooled HRV groups and in each HRV vaccine group (2.0–2.6%) as compared to the placebo group (3.7%). The percentages of subjects reporting severe RV GE tended to be lower in the pooled HRV groups and in each HRV vaccine group (0.4–0.9%) as compared to the placebo group (1.9%).

Stool analysis results were not available for 25% of the reported GE cases due to stool samples not collected during GE episodes or RV ELISA test not performed or invalid result.

Among RV GE episodes reported from day of Dose 1 till Day 14 after Dose 2, G1 vaccine strain RV was detected in 28.6–46.2% RV GE episodes in the HRV vaccine groups. In addition, G1 wild-type, G2 and G9 types were also isolated in the HRV vaccine groups. RV G type could not be identified/was not tested for two subjects in the $10^{4.7}$ ffu HRV vaccine group, three subjects in the $10^{5.2}$ ffu HRV vaccine group and two subjects in the $10^{5.8}$ ffu HRV vaccine group. The serotypes identified in the placebo group were wild-type G1 (50% of RV GE episodes), G9 (40% of RV GE episodes) and G2 (10% of RV GE episodes). From day of Dose 1 till Day 14 after Dose 2, severe RV GE episodes attributed to the G1 vaccine strain were reported infrequently (two subjects in the $10^{5.2}$ ffu HRV vaccine group and one subject in the $10^{5.8}$ ffu HRV vaccine group).

Supplement 41 presents vaccine efficacy against any and severe RV GE during the period starting from day of Dose 1 till Day 14 of Dose 2. Supplement 41 did not include RV GE episodes caused by the vaccine strain RV. The percentages of subjects reporting RV GE (any and severe intensity), caused by RV other than the vaccine strain, tended to be lower in the pooled HRV groups and in each HRV vaccine group as compared to the placebo group. Vaccine efficacy for the pooled HRV vaccine groups was 63.5% [95% CI, 29.5– 81.0] against any RV GE and 73.4% [95% CI, 25.3–90.9] against severe RV GE. These results were similar with those observed for the efficacy from day of Dose 1 till the end of the first efficacy follow-up period and from 2 weeks post Dose 2 till the end of the first efficacy follow-up period.

Occurrence of RV GE from day of Dose 1 till the end of the first efficacy follow-up period

Of the 2155 subjects enrolled in the study, 99 subjects received only one dose of HRV vaccine or placebo and the remaining received two doses of HRV vaccine or placebo (see Table 19). The vaccine efficacy from day of Dose 1 till the end of the first efficacy follow-up period is the efficacy for subjects receiving at least one dose of HRV vaccine or placebo but taking into account also the RV GE episodes that occurred from the day of Dose 1 till Day 14 of Dose 2. This analysis thus considers the effect of the first dose by looking at the number of RV GE episodes occuring between Dose 1 and Dose 2 in vaccine groups *versus* placebo.

Stool analysis results were not available for 26% of the reported GE cases due to stool samples not collected during GE episodes or RV ELISA test not performed or invalid result.

Analysis of RV GE occurring from day of Dose 1 till the end of the first efficacy follow-up period excluded all RV GE episodes caused by the vaccine strain RV.

Supplement 42 presents vaccine efficacy against any and severe RV GE during the period starting from day of Dose 1 till the end of the first efficacy follow-up period.

There was a statistically significant decrease in the percentage of subjects reporting RV GE (any and severe intensity) in pooled HRV groups and in each HRV group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test). Vaccine efficacy for the pooled HRV vaccine groups was 64.2% [95% CI, 50.3–74.1] against any RV GE and 76.1% [95% CI, 62.6–84.9] against severe RV GE. These results were similar with those observed for the efficacy from 2 weeks post Dose 2 till the end of the first efficacy follow-up period.

6 Analysis of safety in subjects planned to receive two doses of HRV vaccine or placebo

6.1 Data sets analyzed

Analysis of safety was performed on the total vaccinated cohort (primary analysis) and the ATP cohort for safety analysis since more than 5% of subjects were eliminated from the ATP cohort for safety analysis. See Section 3.15.4 for description of analyses cohorts and Section 4.2.3 for explanation of eligibility for analysis.

6.2 Total vaccinated cohort for safety analysis

The total vaccinated cohort for analysis of safety consisted of 2155 subjects (538 subjects in the $10^{4.7}$ ffu HRV vaccine group, 540 subjects in the $10^{5.2}$ ffu HRV vaccine group, 540 subjects in the $10^{5.8}$ ffu HRV vaccine group and 537 subjects the placebo group).

Table 19 presents the exposure to vaccination by group and overall.

Table 19: Number and percentage of subjects who received vaccine dose(s) (total vaccinated cohort for safety analysis)

Total number of doses received	HRV $10^{4.7}$ (N = 538)		HRV $10^{5.2}$ (N = 540)		HRV $10^{5.8}$ (N = 540)		Placebo (N = 537)		Total (N = 2155)	
	n	%	n	%	n	%	n	%	n	%
0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
1	28	5.2	31	5.7	25	4.6	15	2.8	99	4.6
2	510	94.8	509	94.3	515	95.4	522	97.2	2056	95.4
Any	538	100	540	100	540	100	537	100	2155	100

Notes: N = number of subjects in each group or in total (sum of all groups)
n/% = number/percentage of subjects receiving the specified total number of doses of HRV vaccine or placebo in each group or in total
Any = number and percentage of subjects receiving at least one dose of HRV vaccine or placebo

Of the 99 subjects who received only one dose of HRV vaccine or placebo, one subject was a drop out due to SAE (death unrelated to vaccination), one subject was a drop out due to vaccination-related non-serious AE, two subjects were drop outs due to vaccination-unrelated non-serious AE and 45 subjects were drop outs due to consent withdrawal. Refer to Section 4.2.2 and Section 6.2.6.2 for further details on these subjects.

6.2.1 Overall incidence of symptoms

Table 20 presents the percentages of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15-day solicited follow-up period.

The majority of subjects in each group reported symptoms (solicited or unsolicited) during the 15-day solicited follow-up period. It should be noted that the majority (more than 98%) of subjects received routine DTPw-HB+Hib vaccine concomitantly with HRV vaccine or placebo and DTPw-based vaccines are known to be highly reactogenic. The incidence rates were similar between groups with very narrow and overlapping 95% CIs. Incidences of symptoms rated as grade "3" in intensity and those assessed as related to vaccination were also similar between the groups. There was no increase in incidence of symptoms (solicited or unsolicited) with subsequent doses of HRV vaccine or with increased viral concentration.

Table 20: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15-day solicited follow-up period (total vaccinated cohort for safety analysis)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	HRV $10^{4.7}$	538	490	91.1	88.3	93.3
	HRV $10^{5.2}$	540	491	90.9	88.2	93.2
	HRV $10^{5.8}$	540	495	91.7	89.0	93.9
	Pooled HRV groups	1618	1476	91.2	89.7	92.6
	Placebo	537	500	93.1	90.6	95.1
Dose 2	HRV $10^{4.7}$	510	437	85.7	82.3	88.6
	HRV $10^{5.2}$	509	449	88.2	85.1	90.9
	HRV $10^{5.8}$	515	451	87.6	84.4	90.3
	Pooled HRV groups	1534	1337	87.2	85.4	88.8
	Placebo	522	457	87.5	84.4	90.3
Overall/dose	HRV $10^{4.7}$	1048	927	88.5	86.4	90.3
	HRV $10^{5.2}$	1049	940	89.6	87.6	91.4
	HRV $10^{5.8}$	1055	946	89.7	87.7	91.4
	Pooled HRV groups	3152	2813	89.2	88.1	90.3
	Placebo	1059	957	90.4	88.4	92.1
Overall/subject	HRV $10^{4.7}$	538	514	95.5	93.4	97.1
	HRV $10^{5.2}$	540	516	95.6	93.5	97.1
	HRV $10^{5.8}$	540	515	95.4	93.2	97.0
	Pooled HRV groups	1618	1545	95.5	94.4	96.4
	Placebo	537	521	97.0	95.2	98.3

Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For each dose:
N = number of subjects having received the considered dose of HRV vaccine or placebo
n/% = number/percentage of subjects reporting at least one symptom for the considered dose of HRV vaccine or placebo
For overall/dose:
N = total number of doses of HRV vaccine or placebo administered
n/% = total number/percentage of doses of HRV vaccine or placebo reporting at least one symptom
For overall/subject:
N= number of subjects having received at least one dose of HRV vaccine or placebo
n/%= number percentage of subjects reporting at least one symptom

Supplement 43 and Supplement 44 respectively present the percentage of doses and of subjects reporting grade "3" and related symptoms (solicited or unsolicited) during the 15-day solicited follow-up period.

6.2.2 Solicited signs and symptoms

Table 21 and Table 22 present the percentage of subjects with specific solicited symptoms including those graded "2 or 3" in intensity, those graded "3" in intensity and those considered to be related to vaccination, during the 15-day solicited follow-up period after each dose of HRV vaccine or placebo.

Supplement 45 presents the percentage of doses and subjects reporting specific solicited symptoms including those graded "2 or 3" in intensity, those graded "3" in intensity and those considered to be related to vaccination, during the 15-day solicited follow-up period after any doses of HRV vaccine or placebo.

Cough/runny nose, fever and irritability were the most commonly reported solicited symptoms in all groups. Diarrhea was the least frequently reported solicited general symptom. Incidences were similar between the groups for each solicited symptom including those rated as grade "2 or 3" in intensity, rated as grade "3" in intensity and those assessed as related to vaccination. There was no apparent increase in incidence of solicited symptoms after Dose 2 as compared to Dose 1 of HRV vaccine or placebo.

*Table 21: Percentage of subjects with each solicited symptom including those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period **after Dose 1** of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Solicited symptom		**HRV $10^{4.7}$ N = 538**				**HRV $10^{5.2}$ N = 540**				**HRV $10^{5.8}$ N = 540**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**			**LL**	**UL**
Cough/ runny nose	Total	325	60.4	56.1	64.6	316	58.5	54.2	62.7	322	59.6	55.4	63.8
	Grade 2 or 3	171	31.8	27.9	35.9	150	27.8	24.0	31.8	167	30.9	27.0	35.0
	Grade 3	45	8.4	6.2	11.0	51	9.4	7.1	12.2	53	9.8	7.4	12.6
	Related	109	20.3	16.9	23.9	102	18.9	15.7	22.4	91	16.9	13.8	20.3
Diarrhea	Total	33	6.1	4.3	8.5	34	6.3	4.4	8.7	44	8.1	6.0	10.8
	Grade 2 or 3	19	3.5	2.1	5.5	24	4.4	2.9	6.5	28	5.2	3.5	7.4
	Grade 3	8	1.5	0.6	2.9	11	2.0	1.0	3.6	11	2.0	1.0	3.6
	Related	16	3.0	1.7	4.8	20	3.7	2.3	5.7	29	5.4	3.6	7.6
Irritability/ fussiness	Total	381	70.8	66.8	74.6	380	70.4	66.3	74.2	391	72.4	68.4	76.1
	Grade 2 or 3	251	46.7	42.4	51.0	241	44.6	40.4	48.9	259	48.0	43.7	52.3
	Grade 3	65	12.1	9.4	15.1	69	12.8	10.1	15.9	75	13.9	11.1	17.1
	Related	236	43.9	39.6	48.2	227	42.0	37.8	46.3	241	44.6	40.4	48.9
Loss of appetite	Total	170	31.6	27.7	35.7	176	32.6	28.7	36.7	171	31.7	27.8	35.8
	Grade 2 or 3	50	9.3	7.0	12.1	50	9.3	7.0	12.0	70	13.0	10.2	16.1
	Grade 3	6	1.1	0.4	2.4	7	1.3	0.5	2.7	11	2.0	1.0	3.6
	Related	74	13.8	11.0	17.0	78	14.4	11.6	17.7	78	14.4	11.6	17.7
Fever	Total	331	61.5	57.3	65.7	339	62.8	58.5	66.9	332	61.5	57.2	65.6
	Grade 2 or 3	127	23.6	20.1	27.4	110	20.4	17.1	24.0	126	23.3	19.8	27.1
	Grade 3	6	1.1	0.4	2.4	7	1.3	0.5	2.7	8	1.5	0.6	2.9
	Related	205	38.1	34.0	42.4	189	35.0	31.0	39.2	189	35.0	31.0	39.2
Vomiting	Total	88	16.4	13.3	19.8	106	19.6	16.4	23.2	91	16.9	13.8	20.3
	Grade 2 or 3	35	6.5	4.6	8.9	61	11.3	8.8	14.3	43	8.0	5.8	10.6
	Grade 3	12	2.2	1.2	3.9	25	4.6	3.0	6.8	22	4.1	2.6	6.1
	Related	48	8.9	6.7	11.7	46	8.5	6.3	11.2	40	7.4	5.3	10.0

Notes: N = number of subjects having received Dose 1 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 1 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

*Table 21 (continued): Percentage of subjects with each solicited symptom including those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period **after Dose 1** of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Solicited symptom		**Pooled HRV groups N = 1618**				**Placebo N = 537**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
Cough/ runny nose	Total	963	59.5	57.1	61.9	340	63.3	59.1	67.4
	Grade 2 or 3	488	30.2	27.9	32.5	182	33.9	29.9	38.1
	Grade 3	149	9.2	7.8	10.7	34	6.3	4.4	8.7
	Related	302	18.7	16.8	20.7	105	19.6	16.3	23.2
Diarrhea	Total	111	6.9	5.7	8.2	45	8.4	6.2	11.1
	Grade 2 or 3	71	4.4	3.4	5.5	27	5.0	3.3	7.2
	Grade 3	30	1.9	1.3	2.6	10	1.9	0.9	3.4
	Related	65	4.0	3.1	5.1	23	4.3	2.7	6.4
Irritability/ fussiness	Total	1152	71.2	68.9	73.4	408	76.0	72.1	79.5
	Grade 2 or 3	751	46.4	44.0	48.9	272	50.7	46.3	55.0
	Grade 3	209	12.9	11.3	14.6	82	15.3	12.3	18.6
	Related	704	43.5	41.1	46.0	243	45.3	41.0	49.6
Loss of appetite	Total	517	32.0	29.7	34.3	187	34.8	30.8	39.0
	Grade 2 or 3	170	10.5	9.1	12.1	65	12.1	9.5	15.2
	Grade 3	24	1.5	1.0	2.2	8	1.5	0.6	2.9
	Related	230	14.2	12.5	16.0	87	16.2	13.2	19.6
Fever	Total	1002	61.9	59.5	64.3	346	64.4	60.2	68.5
	Grade 2 or 3	363	22.4	20.4	24.5	126	23.5	19.9	27.3
	Grade 3	21	1.3	0.8	2.0	11	2.0	1.0	3.6
	Related	583	36.0	33.7	38.4	192	35.8	31.7	40.0
Vomiting	Total	285	17.6	15.8	19.6	89	16.6	13.5	20.0
	Grade 2 or 3	139	8.6	7.3	10.1	43	8.0	5.9	10.6
	Grade 3	59	3.6	2.8	4.7	13	2.4	1.3	4.1
	Related	134	8.3	7.0	9.7	54	10.1	7.6	12.9

Notes: N = number of subjects having received Dose 1 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 1 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

*Table 22: Percentage of subjects with each solicited symptom including those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period **after Dose 2** of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Solicited symptom		**HRV $10^{4.7}$ N = 510**				**HRV $10^{5.2}$ N = 509**				**HRV $10^{5.8}$ N = 515**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**			**LL**	**UL**
Cough/ runny nose	Total	310	60.8	56.4	65.0	323	63.5	59.1	67.7	334	64.9	60.6	69.0
	Grade 2 or 3	164	32.2	28.1	36.4	163	32.0	28.0	36.3	176	34.2	30.1	38.5
	Grade 3	51	10.0	7.5	12.9	51	10.0	7.6	13.0	56	10.9	8.3	13.9
	Related	97	19.0	15.7	22.7	110	21.6	18.1	25.4	109	21.2	17.7	25.0
Diarrhea	Total	38	7.5	5.3	10.1	34	6.7	4.7	9.2	44	8.5	6.3	11.3
	Grade 2 or 3	29	5.7	3.8	8.1	23	4.5	2.9	6.7	29	5.6	3.8	8.0
	Grade 3	8	1.6	0.7	3.1	12	2.4	1.2	4.1	13	2.5	1.4	4.3
	Related	19	3.7	2.3	5.8	23	4.5	2.9	6.7	21	4.1	2.5	6.2
Irritability/ fussiness	Total	292	57.3	52.8	61.6	303	59.5	55.1	63.8	313	60.8	56.4	65.0
	Grade 2 or 3	163	32.0	27.9	36.2	166	32.6	28.6	36.9	191	37.1	32.9	41.4
	Grade 3	53	10.4	7.9	13.4	43	8.4	6.2	11.2	49	9.5	7.1	12.4
	Related	168	32.9	28.9	37.2	173	34.0	29.9	38.3	177	34.4	30.3	38.6
Loss of appetite	Total	149	29.2	25.3	33.4	146	28.7	24.8	32.8	152	29.5	25.6	33.7
	Grade 2 or 3	67	13.1	10.3	16.4	62	12.2	9.5	15.3	61	11.8	9.2	15.0
	Grade 3	14	2.7	1.5	4.6	16	3.1	1.8	5.1	4	0.8	0.2	2.0
	Related	59	11.6	8.9	14.7	54	10.6	8.1	13.6	53	10.3	7.8	13.2
Fever	Total	275	53.9	49.5	58.3	272	53.4	49.0	57.8	279	54.2	49.8	58.5
	Grade 2 or 3	106	20.8	17.3	24.6	116	22.8	19.2	26.7	114	22.1	18.6	26.0
	Grade 3	9	1.8	0.8	3.3	13	2.6	1.4	4.3	14	2.7	1.5	4.5
	Related	139	27.3	23.4	31.3	127	25.0	21.2	28.9	143	27.8	23.9	31.9
Vomiting	Total	55	10.8	8.2	13.8	69	13.6	10.7	16.8	65	12.6	9.9	15.8
	Grade 2 or 3	27	5.3	3.5	7.6	41	8.1	5.8	10.8	37	7.2	5.1	9.8
	Grade 3	13	2.5	1.4	4.3	21	4.1	2.6	6.2	20	3.9	2.4	5.9
	Related	32	6.3	4.3	8.7	33	6.5	4.5	9.0	23	4.5	2.9	6.6

Notes: N = number of subjects having received Dose 2 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 2 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

*Table 22(continued): Percentage of subjects with each solicited symptom including those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period **after Dose 2** of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Solicited symptom		**Pooled HRV groups N = 1534**				**Placebo N = 522**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
Cough/ runny nose	Total	967	63.0	60.6	65.5	331	63.4	59.1	67.6
	Grade 2 or 3	503	32.8	30.4	35.2	190	36.4	32.3	40.7
	Grade 3	158	10.3	8.8	11.9	46	8.8	6.5	11.6
	Related	316	20.6	18.6	22.7	103	19.7	16.4	23.4
Diarrhea	Total	116	7.6	6.3	9.0	46	8.8	6.5	11.6
	Grade 2 or 3	81	5.3	4.2	6.5	33	6.3	4.4	8.8
	Grade 3	33	2.2	1.5	3.0	15	2.9	1.6	4.7
	Related	63	4.1	3.2	5.2	20	3.8	2.4	5.9
Irritability/ fussiness	Total	908	59.2	56.7	61.7	305	58.4	54.1	62.7
	Grade 2 or 3	520	33.9	31.5	36.3	177	33.9	29.9	38.1
	Grade 3	145	9.5	8.0	11.0	42	8.0	5.9	10.7
	Related	518	33.8	31.4	36.2	164	31.4	27.5	35.6
Loss of appetite	Total	447	29.1	26.9	31.5	149	28.5	24.7	32.6
	Grade 2 or 3	190	12.4	10.8	14.1	69	13.2	10.4	16.4
	Grade 3	34	2.2	1.5	3.1	12	2.3	1.2	4.0
	Related	166	10.8	9.3	12.5	58	11.1	8.5	14.1
Fever	Total	826	53.8	51.3	56.4	288	55.2	50.8	59.5
	Grade 2 or 3	336	21.9	19.9	24.1	96	18.4	15.2	22.0
	Grade 3	36	2.3	1.6	3.2	11	2.1	1.1	3.7
	Related	409	26.7	24.5	29.0	125	23.9	20.3	27.8
Vomiting	Total	189	12.3	10.7	14.1	59	11.3	8.7	14.3
	Grade 2 or 3	105	6.8	5.6	8.2	30	5.7	3.9	8.1
	Grade 3	54	3.5	2.7	4.6	15	2.9	1.6	4.7
	Related	88	5.7	4.6	7.0	24	4.6	3.0	6.8

Notes: N = number of subjects having received Dose 2 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 2 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Incidence of each individual solicited symptom during the first 3 days (Day 0 to Day 2) and during the first 8 days (Day 0 to Day 7) after vaccination were calculated since replication of the vaccine virus peaks during the first 8 days after vaccination ([1]). Incidences by onset of symptoms were similar between the groups, with the majority of symptoms occurring within 8 days after vaccination. Only inferential analyses on percentage of subjects reporting each individual solicited symptom within the 8-day (Days 0 to Day 7) after vaccination are presented in this study report.

Table 23 presents statistical comparisons between groups for percentage of subjects reporting each solicited symptom after any dose of HRV vaccine or placebo.

Statistically significant differences were detected between the HRV $10^{4.7}$ group (8.4%) *versus* the HRV $10^{5.2}$ group (12.4%) with respect to the percentage of subjects reporting grade "2 or 3" vomiting after any dose of HRV vaccine or placebo during an 8-day follow-up period (p-value = 0.036, two-sided Fisher's exact test). No other statistically significant differences were detected for the comparison between the pooled HRV vaccine groups or the three HRV vaccine groups *versus* the placebo group with respect to the incidence of subjects reporting individual solicited symptoms (fever, fussiness/irritability, diarrhea, vomiting, loss of appetite and cough/runny nose) (p-value > 0.05, two-sided Fisher's exact test). Importantly, statistically significant differences were not detected for the clinically important grade "3" symptoms. Any statistically significant differences should be interpreted cautiously since, due to the number of endpoints the differences observed in this study are likely to occur by chance alone.

Table 23: Statistical comparisons between groups for percentage of subjects reporting each solicited symptom after any dose of HRV vaccine or placebo (total vaccinated cohort for safety analysis)

Solicited symptom	Type	Follow-up	p-values			
			HRV $10^{4.7}$ *versus* HRV $10^{5.2}$	HRV $10^{4.7}$ *versus* HRV $10^{5.8}$	HRV $10^{5.2}$ *versus* HRV $10^{5.8}$	Pooled HRV groups *versus* placebo
Cough/ runny nose	Any	Onset 15 days	0.942	0.941	0.883	0.113
	Any	Onset 8 days	0.689	0.946	0.640	0.247
	Related	Onset 8 days	0.639	0.737	0.947	0.956
	Grade 2 or 3	Onset 8 days	0.900	0.380	0.490	0.052
	Grade 3	Onset 8 days	0.638	0.638	1.000	0.085
Diarrhea	Any	Onset 15 days	0.512	0.475	0.171	0.080
	Any	Onset 8 days	0.910	0.386	0.327	0.217
	Related	Onset 8 days	0.899	0.537	0.715	0.688
	Grade 2 or 3	Onset 8 days	1.000	1.000	1.000	0.065
	Grade 3	Onset 8 days	0.234	0.328	1.000	0.369
Irritability/ fussiness	Any	Onset 15 days	0.365	0.195	0.755	0.229
	Any	Onset 8 days	0.381	0.306	0.941	0.224
	Related	Onset 8 days	0.951	0.543	0.503	1.000
	Grade 2 or 3	Onset 8 days	0.761	0.541	0.360	0.051
	Grade 3	Onset 8 days	0.682	0.743	1.000	0.351
Loss of appetite	Any	Onset 15 days	0.760	1.000	0.807	0.424
	Any	Onset 8 days	0.804	0.804	1.000	0.172
	Related	Onset 8 days	0.818	0.644	0.877	0.261
	Grade 2 or 3	Onset 8 days	0.393	0.622	0.178	0.250
	Grade 3	Onset 8 days	0.674	0.519	1.000	0.383
Fever	Any	Onset 15 days	0.468	0.723	0.280	0.213
	Any	Onset 8 days	1.000	0.336	0.372	0.190
	Related	Onset 8 days	0.324	0.460	0.853	0.880
	Grade 2 or 3	Onset 8 days	0.844	0.434	0.603	0.487
	Grade 3	Onset 8 days	0.579	0.707	1.000	0.880
Vomiting	Any	Onset 15 days	0.079	0.474	0.332	0.729
	Any	Onset 8 days	0.291	0.542	0.710	0.711
	Related	Onset 8 days	0.852	0.246	0.380	0.938
	Grade 2 or 3	Onset 8 days	0.036	0.399	0.247	0.742
	Grade 3	Onset 8 days	0.117	0.371	0.593	0.232

Notes: Onset 8 days = onset on Day 0 to Day 7 Onset 15 days = onset on Day 0 to Day 14
Any = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
p-value = results of comparison of percentage of subjects reporting the specified solicited symptom after any doses of HRV vaccine or placebo between groups by two-sided Fisher's exact test (significant level of $\alpha = 0.05$)

Supplement 46 to Supplement 51 present prevalence of diarrhea, vomiting and fever during the 15-day solicited follow-up period after each dose of HRV vaccine or placebo. For all groups, there was no specific day following either dose of HRV vaccine or placebo during which diarrhea or vomiting peaked. A peak in the incidence of fever was observed at Day 0 (day of vaccination) and Day 1 (day after vaccination) for all groups, and could be (at least) in part due to concomitantly administered routine vaccines (DTPw-HB+Hib) as confirmed by the placebo group.

Supplement 52 presents the duration (in days) of diarrhea, vomiting and fever during the solicited follow-up period. Values for mean duration of diarrhea, vomiting and fever during the 15-day solicited follow-up period after each dose of HRV vaccine or placebo were similar between the groups.

6.2.3 Unsolicited symptoms

Supplement 53 presents the percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms from Day 0 to Day 42 after any vaccination. The percentage of subjects reporting at least one unsolicited symptoms from Day 0 to Day 42 after vaccination were similar between the groups: 65.1% in the HRV $10^{4.7}$ group, 65.6% in the HRV $10^{5.2}$ group, 60.7% in the HRV $10^{5.8}$ group and 63.7% in the placebo group.

Table 24 presents the percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from Day 0 to Day 42 after any vaccination. Unsolicited symptoms reported by only six subjects (two subjects in the HRV $10^{4.7}$ group and four subjects in the placebo group), all from Brazil, were assessed as related to vaccination.

*Table 24: The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as **related** to vaccination, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)*

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV $10^{4.7}$ N = 538				HRV $10^{5.2}$ N = 540				HRV $10^{5.8}$ N = 540			
				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		2	0.4	0	1.3	0	0	0	0.7	0	0	0	0.7
Application site (1820)	Injection site reaction (0058)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
	Fever (0725)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7
	Pallor (0220)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
Respiratory system (1100)	Bronchitis (0805)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Comment: At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms

*Table 24 (continued): The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as **related** to vaccination, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)*

WHO Body System (CODE)	**WHO Preferred term (CODE)**	**Pooled HRV groups N = 1618**				**Placebo N = 537**			
				95% CI				**95% CI**	
		s	**%**	**LL**	**UL**	**s**	**%**	**LL**	UL
At least one symptom		2	0.1	0	0.4	4	0.7	0.2	1.9
Application site (1820)	Injection site reaction (0058)	0	0	0	0.2	1	0.2	0	1
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.2	1	0.2	0	1
	Fever (0725)	1	0.1	0	0.3	0	0	0	0.7
	Pallor (0220)	0	0	0	0.2	1	0.2	0	1
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	0.2	1	0.2	0	1
Respiratory system (1100)	Bronchitis (0805)	1	0.1	0	0.3	0	0	0	0.7

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Comment: At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms

Table 25 presents the percentage of subjects with grade 3 unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination. The percentage of subjects with grade "3" unsolicited symptoms from Day 0 to Day 42 after vaccination were similar between the groups.

*Table 25: The percentage of subjects with **grade "3"** unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)*

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV $10^{4.7}$ N = 538				HRV $10^{5.2}$ N = 540				HRV $10^{5.8}$ N = 540			
				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		15	2.8	1.6	4.6	27	5	3.3	7.2	14	2.6	1.4	4.3
Application site (1820)	Dermatitis contact (0049)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7
	Allergic reaction (0712)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
	Death, nos (0722)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1
	Edema generalized (0400)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
	Fever (0725)	0	0	0	0.7	2	0.4	0	1.3	1	0.2	0	1
	Pallor (0220)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
Central and peripheral nervous system (410)	Fever convulsions (1357)	1	0.2	0	1	0	0	0	0.7	1	0.2	0	1
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
Gastrointestinal system (600)	Abdominal pain (0268)	2	0.4	0	1.3	3	0.6	0.1	1.6	1	0.2	0	1
	Anorexia (0165)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7
	Constipation (0204)	0	0	0	0.7	1	0.2	0	1	1	0.2	0	1
	Gastroenteritis (0293)	3	0.6	0.1	1.6	5	0.9	0.3	2.1	1	0.2	0	1
	Gastrointestinal disorder nos (1262)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1
Psychiatric (500)	Nervousness (0188)	1	0.2	0	1	1	0.2	0	1	1	0.2	0	1
Resistance mechanism (1830)	Infection (0736)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7
	Moniliasis (0741)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7
Respiratory system (1100)	Asthma (1367)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7
	Bronchitis (0805)	2	0.4	0	1.3	4	0.7	0.2	1.9	0	0	0	0.7
	Pharyngitis (0523)	3	0.6	0.1	1.6	7	1.3	0.5	2.7	2	0.4	0	1.3
	Pneumonia (0528)	5	0.9	0.3	2.2	8	1.5	0.6	2.9	6	1.1	0.4	2.4

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

*Table 25 (continued): The percentage of subjects with **grade "3"** unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)*

WHO Body System (CODE)	**WHO Preferred term (CODE)**	**Pooled HRV groups N = 1618**				**Placebo N = 537**			
				95% CI				**95% CI**	
		s	**%**	**LL**	**UL**	**s**	**%**	**LL**	UL
At least one symptom		56	3.5	2.6	4.5	17	3.2	1.9	5
Application site (1820)	Dermatitis contact (0049)	1	0.1	0	0.3	0	0	0	0.7
Body as a whole general (1810)	Abdomen enlarged (0711)	1	0.1	0	0.3	0	0	0	0.7
	Allergic reaction (0712)	0	0	0	0.2	1	0.2	0	1
	Death, nos (0722)	1	0.1	0	0.3	0	0	0	0.7
	Edema generalized (0400)	0	0	0	0.2	1	0.2	0	1
	Fever (0725)	3	0.2	0	0.5	0	0	0	0.7
	Pallor (0220)	0	0	0	0.2	1	0.2	0	1
Central and peripheral nervous system (410)	Fever convulsions (1357)	2	0.1	0	0.4	0	0	0	0.7
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.2	1	0.2	0	1
Gastrointestinal system (600)	Abdominal pain (0268)	6	0.4	0.1	0.8	0	0	0	0.7
	Anorexia (0165)	1	0.1	0	0.3	0	0	0	0.7
	Constipation (0204)	2	0.1	0	0.4	0	0	0	0.7
	Gastroenteritis (0293)	9	0.6	0.3	1.1	4	0.7	0.2	1.9
	Gastrointestinal disorder nos (1262)	1	0.1	0	0.3	1	0.2	0	1
Psychiatric (500)	Nervousness (0188)	3	0.2	0	0.5	0	0	0	0.7
Resistance mechanism (1830)	Infection (0736)	1	0.1	0	0.3	1	0.2	0	1
	Moniliasis (0741)	1	0.1	0	0.3	0	0	0	0.7
Respiratory system (1100)	Asthma (1367)	1	0.1	0	0.3	0	0	0	0.7
	Bronchitis (0805)	6	0.4	0.1	0.8	0	0	0	0.7
	Pharyngitis (0523)	12	0.7	0.4	1.3	2	0.4	0	1.3
	Pneumonia (0528)	19	1.2	0.7	1.8	6	1.1	0.4	2.4

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 54, Supplement 55 and Supplement 56 respectively present percentage of doses with all, related and grade 3 unsolicited symptoms from Day 0 to Day 42 after any vaccination.

Supplement 57 and Supplement 58 respectively present the percentage of subjects and doses respectively reporting gastrointestinal symptoms (WHO code 600) from Day 0 to Day 42 after any vaccination. The percentage of subjects and doses reporting any and grade "3" gastrointestinal symptoms (WHO code 600) from Day 0 to Day 42 after vaccination were low and similar between the groups. None of the gastrointestinal symptoms were assessed as related to vaccination.

6.2.4 Concomitant medications

Percentages of subjects who took medications during the study were similar between the groups. During the study (with start date between Dose 1 of HRV vaccine or placebo and visit at the end of the first efficacy follow-up period), 476 subjects (88.5%) in the HRV $10^{4.7}$ group, 480 subjects (88.9%) in the HRV $10^{5.2}$ group, 484 subjects (89.6%) in the HRV $10^{5.8}$ group and 488 subjects (90.9%) in the placebo group took at least one medication.

Table 26 presents the percentage of doses with at least one concomitant medication administered from Day 0 to Day 14 after vaccination, by type. Supplement 59 presents the percentage of overall doses and subjects with at least one concomitant medication administered from Day 0 to Day 14 after any vaccination, by type.

Concomitant medications were administered to 428 subjects (79.6%) in the HRV $10^{4.7}$ group, 446 subjects (82.6%) in the HRV $10^{5.2}$ group, 430 subjects (79.6%) in the HRV $10^{5.8}$ group and 446 subjects (83.1%) in the placebo group from Day 0 to Day 14 after vaccination. The majority of subjects in each group received antipyretics from Day 0 to Day 14 after vaccination and percentages of subjects who took antipyretics were similar between the groups. There was no increase in the percentage of subjects who took medications after Dose 2 as compared to Dose 1 of HRV vaccine or placebo.

Table 26: Percentage of doses with at least one concomitant medication administered from Day 0 to Day 14 after vaccination, by type (total vaccinated cohort for safety analysis)

	Dose 1											
	HRV $10^{4.7}$ (N=538)				HRV $10^{5.2}$ (N=540)				HRV $10^{5.8}$ (N=540)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL			LL	UL
Any medication	346	64.3	60.1	68.4	355	65.7	61.6	69.7	361	66.9	62.7	70.8
Any antipyretic	342	63.6	59.3	67.6	343	63.5	59.3	67.6	355	65.7	61.6	69.7
Prophylactic antipyretic	69	12.8	10.1	15.9	69	12.8	10.1	15.9	80	14.8	11.9	18.1
Any antibiotic	6	1.1	0.4	2.4	15	2.8	1.6	4.5	10	1.9	0.9	3.4

	Pooled HRV groups (N=1618)				Placebo (N=537)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL
Any medication	1062	65.6	63.3	68.0	382	71.1	67.1	74.9
Any antipyretic	1040	64.3	61.9	66.6	372	69.3	65.2	73.2
Prophylactic antipyretic	218	13.5	11.8	15.2	74	13.8	11.0	17.0
Any antibiotic	31	1.9	1.3	2.7	15	2.8	1.6	4.6

	Dose 2											
	HRV $10^{4.7}$ (N=510)				HRV $10^{5.2}$ (N=509)				HRV $10^{5.8}$ (N=515)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL			LL	UL
Any medication	306	60.0	55.6	64.3	329	64.6	60.3	68.8	302	58.6	54.3	62.9
Any antipyretic	298	58.4	54.0	62.7	321	63.1	58.7	67.3	292	56.7	52.3	61.0
Prophylactic antipyretic	55	10.8	8.2	13.8	65	12.8	10.0	16.0	50	9.7	7.3	12.6
Any antibiotic	19	3.7	2.3	5.8	28	5.5	3.7	7.9	16	3.1	1.8	5.0

	Pooled HRV groups (N=1534)				Placebo (N=522)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL				
Any medication	937	61.1	58.6	63.5	318	60.9	56.6	65.1
Any antipyretic	911	59.4	56.9	61.9	310	59.4	55.0	63.6
Prophylactic antipyretic	170	11.1	9.6	12.8	56	10.7	8.2	13.7
Any antibiotic	63	4.1	3.2	5.2	15	2.9	1.6	4.7

Notes: For each dose:
N = number of subjects having received the considered dose of HRV vaccine or placebo
n/% = number/percentage of subjects who started taking the specified concomitant medication at least once from Day 0 to Day 14 after the considered dose of HRV vaccine or placebo
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 60 and Supplement 61 present the percentage of subjects who took antipyretics by day, from Day 0 to Day 42, respectively after Dose 1 and Dose 2 of HRV vaccine or placebo. The percentage of subjects who took antipyretics peaked on Day 0 and Day 1 of each dose in all groups (HRV vaccine or placebo with concomitant DTPw-HB+Hib vaccine).

6.2.5 Reactogenicity analysis by country

Supplement 62 to Supplement 87 present reactogenicity results by country for the total vaccinated cohort.

For each country, the incidences of any symptoms (solicited or unsolicited) during the 15-day solicited follow-up period, including grade "3" and related symptoms, were similar between the groups.

Although some differences in incidence rates of specific solicited symptoms were observed between the countries, the incidence rates were similar between the HRV vaccine groups and the placebo within each country. Country-specific customs and practices could account for the observed differences between countries. Difference in incidence of solicited symptoms was marked for some solicited symptoms. For example, the incidence of irritability, a subjective symptom, was lower in Venezuela (65–72%) than in Brazil (89–93%) and in Mexico (86–92%). On the other hand, the incidence of fever, a symptom whose evaluation is quantitative, was similar between the countries. Incidences of symptoms assessed as related to vaccination were higher in Brazil and in Mexico than in Venezuela. Also, related unsolicited symptoms were reported only in Brazil. Since attribution of the relationship is done by the respective investigators, country-specific practices could again account for the observed differences.

Overall, results of the reactogenicity analyses by country were the same as the global reactogenicity analysis with the reactogenicity profile of each viral concentration of HRV vaccine similar to that of the placebo in terms of the incidences of solicited and unsolicited symptoms reported after vaccination.

6.2.6 Serious adverse events

Appendix: Serious Adverse Events presents a summary table for the SAEs reported until the end of the first efficacy follow-up period and the clinical narratives for all SAEs reported until the end of the first efficacy follow-up period.

Among the subjects planned to receive two doses of HRV vaccine or placebo, 220 subjects (52 in the HRV $10^{4.7}$ group, 55 in the HRV $10^{5.2}$ group, 49 in the HRV $10^{5.8}$ group and 64 in the placebo group) reported at least one SAE until the end of the first efficacy follow-up period.

All SAEs reported until the end of the first efficacy follow-up period among the subjects planned to receive two doses of HRV vaccine or placebo were assessed as not related to study vaccination (HRV vaccine or placebo) by the respective investigators.

6.2.6.1 SAEs assessed as possibly related to the concomitantly administered routine vaccination

One SAE was assessed as possibly related to the concomitantly administered routine vaccination by the respective investigator. Description of this SAE is given below:

- [redacted]

6.2.6.2 SAEs with fatal outcome

Three fatalities were reported during the study. All of the deaths were assessed as not related to vaccination by the respective investigators. Summary of these cases is presented below.

- [redacted]
- [redacted]

- [redacted]

6.2.6.3 IS

One IS case was reported during the study and was assessed as not related to the vaccination. Description of the IS case is given below:

- [redacted]

6.2.6.4 SAEs ongoing at the data lock point for analysis

Four SAEs (cerebral palsy in one subject, retarded psychomotor development in two subjects and anemia in one subject) were ongoing at the end of the first efficacy follow-up period. Three of the subjects (two with cerebral palsy and one with retarded psychomotor development) did not require hospitalization but the cases were reported as SAEs because they were considered medically important by the respective investigators. All four SAEs were assessed as not related to vaccination.

6.3 ATP cohort for safety analysis

The ATP cohort for safety analysis consisted of 1965 subjects (499 subjects in the $10^{4.7}$ ffu HRV vaccine group, 487 subjects in the $10^{5.2}$ ffu HRV vaccine group, 493 subjects in the $10^{5.8}$ ffu HRV vaccine group and 486 subjects the placebo group).

Supplement 88 to Supplement 98 present reactogenicity results for the ATP cohort.

The results of the ATP safety cohort analyses were consistent with those observed in the total vaccinated cohort analyses.

7 Analysis of immunogenicity in subjects planned to receive two doses of HRV vaccine or placebo

7.1 Data sets analyzed

Analysis of immunogenicity was performed on the ATP cohort (primary analysis) and the total vaccinated cohort. See Section 3.15.4 for definition of cohorts identified for analyses and Section 4.2.3 for description of eligibility for analyses.

7.2 ATP cohort for immunogenicity analysis

The ATP cohort for immunogenicity analysis consisted of 1526 subjects (395 subjects in the $10^{4.7}$ ffu HRV vaccine group, 377 subjects in the $10^{5.2}$ ffu HRV vaccine group, 381 subjects in the $10^{5.8}$ ffu HRV vaccine group and 373 subjects the placebo group).

7.2.1 Immunogenicity of the HRV vaccine

Anti-rotavirus IgA antibody GMCs and seropositivity rates at each sampling timepoint are presented in Table 27.

Seroconversion rates in the three vaccine groups were similar at each post-vaccination timepoint. A trend toward higher anti-rotavirus IgA antibody GMCs at two months after Dose 2 of HRV vaccine or placebo was observed in the $10^{5.8}$ ffu HRV vaccine group as compared to the other vaccine groups. At the end of the first efficacy follow-up period, persistence of anti-rotavirus IgA antibodies in terms of seropositivity rate and GMCs was similar in the three vaccine groups.

Table 27: Anti-rotavirus IgA antibody GMCs and seropositivity rates (ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 20 U/ml				GMC (U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	Pre	395	0	0.0	0.0	0.9	<20.0	-	-
	PI(M2)	146	57	39.0	31.1	47.5	27.0	21.5	33.9
	PII(M4)	142	86	60.6	52.0	68.7	54.0	40.9	71.2
	PII(M10)	377	275	72.9	68.2	77.4	78.9	66.7	93.2
HRV $10^{5.2}$	Pre	374	0	0.0	0.0	1.0	<20.0	-	-
	PI(M2)	127	48	37.8	29.3	46.8	23.9	19.1	30.0
	PII(M4)	125	78	62.4	53.3	70.9	52.1	39.7	68.3
	PII(M10)	359	273	76.0	71.3	80.4	85.0	72.1	100.2
HRV $10^{5.8}$	Pre	377	0	0.0	0.0	1.0	<20.0	-	-
	PI(M2)	132	57	43.2	34.6	52.1	32.2	24.8	41.8
	PII(M4)	124	81	65.3	56.3	73.6	70.7	51.9	96.3
	PII(M10)	354	273	77.1	72.4	81.4	81.8	70.1	95.6
Placebo	Pre	368	0	0.0	0.0	1.0	<20.0	-	-
	PI(M2)	139	3	2.2	0.4	6.2	<20.0	-	-
	PII(M4)	132	7	5.3	2.2	10.6	<20.0	-	-
	PII(M10)	360	149	41.4	36.3	46.7	43.2	35.4	52.8

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Pre = pre-vaccination
PI(M2) = blood sample taken two months after Dose 1 of HRV vaccine or placebo
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period
Comment: The seroconversion rate was the seropositivity rate at the post-vaccination sampling timepoint in subjects initially negative for RV (for the ATP cohort, at post Dose 1 and post Dose 2 time point, seroconversion rate = seropositivity rate).

Supplement 99 and Supplement 100 respectively present reverse cumulative distribution curves of anti-rotavirus IgA antibody concentrations in the HRV vaccine group two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Table 28 presents seroconversion rate on combined doses. Seroconversion rates on combined doses were similar in the three vaccine groups.

Table 28: Anti-rotavirus IgA antibody seroconversion rates on combined doses (ATP cohort for immunogenicity analysis)

Group	N	Seroconversion on combined Dose 1 and Dose 2 at Visit 3			
				95% CI	
		n	%	LL	UL
HRV $10^{4.7}$	145	89	61.4	52.9	69.3
HRV $10^{5.2}$	130	86	66.2	57.3	74.2
HRV $10^{5.8}$	127	85	66.9	58.0	75.0
Placebo	132	7	5.3	2.2	10.6

Notes: N = number of subjects with available anti-rotavirus IgA antibody results at Visit 3 and/or with seroconversion at Visit 2
n/% = number/percentage of subjects who seroconverted at Visit 2 or Visit 3
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

The anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies are presented in Table 29. Results show that the GMCs induced by the vaccine are lower than the GMCs induced by the natural infection in the placebo group.

Table 29: Anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity analysis)

Group	Timing		GMC (U/ml)		
			Value	95% CI	
		N		LL	UL
HRV $10^{4.7}$	PI(M2)	57	127.1	97.5	165.6
	PII(M4)	86	161.7	124.2	210.6
	PII(M10)	275	169.6	146.4	196.6
HRV $10^{5.2}$	PI(M2)	48	100.6	75.2	134.5
	PII(M4)	78	140.7	111.0	178.5
	PII(M10)	273	166.8	144.8	192.1
HRV $10^{5.8}$	PI(M2)	57	150.4	113.7	198.8
	PII(M4)	81	199.6	152.4	261.5
	PII(M10)	273	152.7	134.4	173.5
Placebo	PI(M2)	3	327.3	3.6	29783.1
	PII(M4)	7	464.9	81.0	2668.1
	PII(M10)	149	343.3	278.4	423.4

Notes: N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PI(M2) = blood sample taken two months after Dose 1 of HRV vaccine or placebo
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

7.2.2 Immunogenicity of the HRV vaccine in the stool analysis subset

Refer to Section 3.7.3 for definition of the stool analysis subset.

Anti-rotavirus IgA antibody GMCs and seropositivity rates at each sampling timepoint are presented in Table 30.

Seroconversion rates in the three vaccine groups were similar at each post-vaccination timepoint. A trend toward higher anti-rotavirus IgA antibody GMCs at two months after Dose 2 of HRV vaccine or placebo was observed in the $10^{5.8}$ ffu HRV vaccine group as compared to the other vaccine groups. At the end of the first efficacy follow-up period, persistence of anti-rotavirus IgA antibodies in terms of seropositivity rate and GMCs was similar in the three vaccine groups.

Table 30: Anti-rotavirus IgA antibody GMCs and seropositivity rate (stool analysis subset, ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 20 U/ml				GMC (U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	Pre	118	0	0.0	0.0	3.1	<20.0	-	-
	PI(M2)	104	44	42.3	32.7	52.4	30.3	22.8	40.3
	PII(M4)	104	65	62.5	52.5	71.8	57.3	41.3	79.7
	PII(M10)	106	82	77.4	68.2	84.9	104.1	75.2	144.3
HRV $10^{5.2}$	Pre	112	0	0.0	0.0	3.2	<20.0	-	-
	PI(M2)	94	33	35.1	25.5	45.6	21.7	17.0	27.8
	PII(M4)	96	58	60.4	49.9	70.3	51.9	37.9	71.2
	PII(M10)	97	67	69.1	58.9	78.1	70.7	51.1	97.8
HRV $10^{5.8}$	Pre	111	0	0.0	0.0	3.3	<20.0	-	-
	PI(M2)	97	42	43.3	33.3	53.7	33.7	24.5	46.3
	PII(M4)	93	59	63.4	52.8	73.2	65.8	46.0	94.2
	PII(M10)	92	66	71.7	61.4	80.6	81.7	58.4	114.2
Placebo	Pre	104	0	0.0	0.0	3.5	<20.0	-	-
	PI(M2)	105	0	0.0	0.0	3.5	<20.0	-	-
	PII(M4)	99	4	4.0	1.1	10.0	<20.0	-	-
	PII(M10)	97	39	40.2	30.4	50.7	44.0	29.5	65.5

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Pre = pre-vaccination
PI(M2) = blood sample taken two months after Dose 1 of HRV vaccine or placebo
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period
Comment: The seroconversion rate was the seropositivity rate at the post-vaccination sampling timepoint in subjects initially negative for RV (for the ATP cohort, at post Dose 1 and post Dose 2 time point, seroconversion rate = seropositivity rate).

Table 31 presents the number of subjects with vaccine virus in stool samples collected at pre-determined timepoints.

The percentages of vaccinees with RV shedding between Day 6 and Day 10 after Dose 1 of HRV vaccine or placebo ranged from 35.2% to 44.1% between the vaccine groups. RV shedding between Day 6 and Day 10 after Dose 1 of HRV vaccine or placebo tended to be higher in the $10^{5.8}$ ffu HRV vaccine group as compared to the other vaccine groups.

None of the stool samples collected on the day of Dose 2 of HRV vaccine or placebo (approximately 2 months after Dose 1 of HRV vaccine or placebo) were RV positive, except for a stool sample from one subject in the $10^{5.8}$ ffu HRV vaccine group.

The percentages of vaccinees with RV shedding between Day 6 and Day 10 after Dose 2 of HRV vaccine or placebo ranged from 11.5% to 21.3% between the vaccine groups.

The RV type was analysed for subjects in the placebo group who shed RV after vaccination. None of the placebo recipients in the ATP immunogenicity cohort shed RV, except one subject who shed wild-type G2 RV. Three more placebo recipients who were eliminated from the ATP cohort also shed RV: RV isolate from one subject was the G1 vaccine strain at Day 60 and RV isolate from two subjects were non vaccine strains (G9 and wild-type G1).

Table 31: Number of subjects with vaccine virus in stool samples collected at pre-determined timepoints (ATP cohort for immunogenicity analysis)

Group	Shedding Dose 1								
	Day 0 [Day –1 to Day 0]			[Day 1 to Day 5]			Day 7 [Day 6 to Day 10]		
	N	n	%	N	n	%	N	n	%
HRV $10^{4.7}$	110	0	0.0	1	0	0.0	105	38	36.2
HRV $10^{5.2}$	100	0	0.0	1	0	0.0	105	37	35.2
HRV $10^{5.8}$	103	0	0.0	3	0	0.0	102	45	44.1
Placebo	98	0	0.0	2	0	0.0	96	0	0.0

Group	Shedding Dose 1					
	[Day 11 to Day 12]			Day 60 [Day –2 to Day 0 of Dose 2]		
	N	n	%	N	n	%
HRV $10^{4.7}$	0	-	-	100	0	0.0
HRV $10^{5.2}$	1	0	0.0	93	0	0.0
HRV $10^{5.8}$	2	0	0.0	91	1	1.1
Placebo	0	-	-	96	0	0.0

Group	Shedding Dose 2								
	[Day 1 to Day 5]			Day 7 [Day 6 to Day 10]			[Day 11 to Day 15]		
	N	n	%	N	n	%	N	n	%
HRV $10^{4.7}$	6	0	0.0	87	10	11.5	5	0	0.0
HRV $10^{5.2}$	4	1	25.0	89	19	21.3	2	0	0.0
HRV $10^{5.8}$	6	1	16.7	91	15	16.5	4	0	0.0
Placebo	2	0	0.0	93	1	1.1	1	0	0.0

Notes: N = number of subject with available stool results at the specified time point
n/% = number/percentage of subjects with rotavirus in stool collected at the specified time point

Table 32 presents percentage of subjects with vaccine virus in stool samples collected at pre-determined time points on combined doses. There was a trend towards lower percentage of subjects in the $10^{4.7}$ ffu HRV vaccine group shedding vaccine virus.

Table 32: Percentage of subjects with vaccine virus in stool samples collected at pre-determined time points, on combined time points (ATP cohort for immunogenicity analysis)

Group	Shedding – combined timepoints				
	N	n	%	95%CI	
				L.L.	U.L.
HRV $10^{4.7}$	118	45	38.1	29.4	47.5
HRV $10^{5.2}$	115	52	45.2	35.9	54.8
HRV $10^{5.8}$	115	55	47.8	38.4	57.3
Placebo	109	1	0.9	0.0	5.0

Notes: N = number of subject with available stool results for at least one time point
n/% = number/percentage of subjects with rotavirus in at least one stool
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 33 presents the percentage of subjects with vaccine take after each dose of HRV vaccine or placebo. Refer to Section 3.15.8.1 for rules on calculating vaccine take. There was a trend towards higher percentage of subjects in the $10^{5.8}$ ffu HRV vaccine group with vaccine take.

Table 33: Percentage of subjects with vaccine take after each dose of HRV vaccine or placebo (ATP cohort for immunogenicity analysis)

Group	Vaccine take after Dose 1, at Visit 2					Vaccine take after Dose 2, at Visit 3				
				95%CI				%	95%CI	
	N	n	%	L.L.	U.L.	N	n	%	L.L.	U.L.
HRV $10^{4.7}$	105	51	48.6	38.7	58.5	104	66	63.5	53.4	72.7
HRV $10^{5.2}$	105	52	49.5	39.6	59.5	99	62	62.6	52.3	72.1
HRV $10^{5.8}$	108	62	57.4	47.5	66.9	97	67	69.1	58.9	78.1
Placebo	105	0	0.0	0.0	3.5	99	4	4.0	1.1	10.0

Notes: *Dose 1:*
N = number of subject with available anti-rotavirus IgA antibody results at Visit 2 or with vaccine virus* in stools collected from after Visit 1 to Visit 2
n/% = number/percentage of subjects who seroconverted at Visit 2 or with vaccine virus* in stools collected after Visit 1 to Visit 2
Dose 2 – Visit 3:
N = number of subject with available anti-rotavirus IgA antibody results at Visit 3 or with vaccine virus* in stools collected after Visit 2 to Visit 3
n/% = number/percentage of subjects who seroconverted at Visit 3 or with vaccine virus* in stools collected after Visit 2 to Visit 3
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Comment: *RV in stools collected at pre-determined time points or vaccine virus in stools collected in case of GE episode

Table 34 presents the percentage of subjects with vaccine take after combined doses. Refer to Section 3.15.8.1 for rules on calculating vaccine take. There was a trend towards lower vaccine take in the $10^{4.7}$ ffu HRV vaccine group.

Table 34: Percentage of subjects with vaccine take after combined doses (ATP cohort for immunogenicity analysis)

Group	Vaccine take on combined Doses 1 and 2, at Visit 3				
				95%CI	
	N	n	%	L.L.	U.L.
HRV $10^{4.7}$	107	69	64.5	54.6	73.5
HRV $10^{5.2}$	109	79	72.5	63.1	80.6
HRV $10^{5.8}$	106	80	75.5	66.2	83.3
Placebo	99	4	4.0	1.1	10.0

Notes: N = number of subjects with available anti-rotavirus IgA antibody result at Visit 3, or who seroconverted at Visit 2, or with vaccine virus* in stools collected after Visit 1 to Visit 3
n/% = number/percentage of subjects who seroconverted at Visit 2 or 3, or with vaccine virus* in stools collected after Visit 1 to Visit 3
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Comment: *RV in stools collected at pre-determined time points or vaccine virus in stools collected in case of GE episode

Table 35 presents the standardized asymptotic 95% CIs for the difference in vaccine take on combined doses 1 and 2 at two months after Dose 2 of HRV vaccine or placebo (at Visit 3) between HRV vaccine and placebo groups.

The lowest value of the lower limit of the standardized asymptotic 95% CI for the difference in the percentage of subjects with vaccine take on combined doses 1 and 2 at two months after Dose 2 of HRV vaccine or placebo (at Visit 3) between each HRV vaccine group and (minus) the placebo group was above 49% indicating that the vaccine take was significantly higher in the HRV vaccine groups as compared to the placebo group.

Table 35: Difference in percentage of subjects with vaccine take on combined doses 1 and 2 at two months after Dose 2 of HRV vaccine or placebo (at Visit 3) between each HRV vaccine and placebo groups (ATP cohort for immunogenicity analysis)

						Difference in vaccine take			
							Value	95 % CI	
Group	**N**	**%**	**Group**	**N**	**%**	**Groups difference**	**(%)**	**L.L**	**U.L**
HRV $10^{4.7}$	107	64.5	Placebo	99	4.0	HRV $10^{4.7}$ - Placebo	60.4	49.9	69.5
HRV $10^{5.2}$	109	72.5				HRV $10^{5.2}$ - Placebo	68.4	58.3	76.7
HRV $10^{5.8}$	106	75.5				HRV $10^{5.8}$- Placebo	71.4	61.3	79.4

Notes: N = number of subjects
% = percentage of subjects with vaccine take on combined Doses 1 and 2, at Visit 3
95% CI = standardized asymptotic Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

7.2.3 Impact of feeding on immunogenicity of HRV vaccine

Supplement 101 presents the results of the logistic regression analysis to determine the impact of feeding on the vaccine take at two months after Dose 2 of HRV vaccine or placebo, on combined doses 1 and 2. None of the pre-defined feeding criteria including type of food and timing of feeding with respect to HRV vaccine dose had a significant effect on the vaccine take (all p-values > 0.1). Therefore, vaccine take rates by feeding criteria were not tabulated.

7.2.4 Immunogenicity analysis by country

Supplement 102, Supplement 103 and Supplement 104 present anti-rotavirus IgA antibody GMCs and seroconversion rates by country. Country-specific variations in immune response were observed. At two months after Dose 2 of HRV vaccine or placebo, the seroconversion rate in the HRV vaccine groups ranged from 54.7–74.4% in Brazil, 50.0–70.6% in Mexico and 60.5–63.0% in Venezuela.

7.2.5 Immunogenicity of routine vaccinations (DTPw-HB+Hib and OPV)

For the ATP cohort for immunogenicity, the majority of subjects (> 98%) in each group received the DTPw-HB+Hib vaccine concomitantly with Dose 1 and Dose 2 of HRV vaccine or placebo. None of the subjects received OPV concomitantly with Dose 1 and Dose 2 of HRV vaccine or placebo. For subjects with available routine vaccination serology results at Visit 3, more than 93% of subjects in each group received two doses of DTPw-HB+Hib and OPV vaccines between Visit 1 and before Visit 3. For subjects with available routine vaccination serology results at the end of the first efficacy follow-up period, more than 94% of subjects in each group received three doses of DTPw-HB+Hib and OPV vaccines between Visit 1 and before the end of the first efficacy follow-up period.

For immunogenicity analyses of routine vaccines, the Study Month 4 (two months after Dose 2 of HRV vaccine or placebo) timepoint reflects the impact of two doses of HRV vaccine, as compared to placebo, on the immune responses of two doses of concomitantly administered routine DTPw-HB+Hib vaccine and two doses of OPV vaccine given separately from the study vaccines. Since the primary course of routine vaccines consists of three doses, the Study Month 10 (at the end of the first efficacy follow-up period) timepoint evaluates any effect of the HRV vaccine on the immunogenicity DTPw-HB+Hib and OPV vaccines after completion of the full routine vaccination course. It should be noted that the immunogenicity data at Study Month 10 are "persistence data" since antibody levels were not measured immediately after completion of the three-dose primary vaccination course of routine vaccines.

Analysis of immunogenicity of routine vaccinations for the ATP cohort was performed on the subset of subjects who had documented receipt of at least two doses of routine vaccines between Visit 1 and before the end of the first efficacy follow-up period.

Two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period, the majority of subjects had seroprotective levels of anti-tetanus, anti-HBs, anti-PRP (≥ 0.15 mcg/ml and ≥ 1 mcg/ml) and anti-poliovirus types 1, 2 and 3 antibodies. The seroprotection rates for anti-diphtheria antibodies ranged from 58.8% to 75.4% two months after Dose 2 of HRV vaccine or placebo and from 68.5% to 74.5% at the end of the first efficacy follow-up period. The seropositivity rates for anti-BPT antibodies ranged from 59.0% to 65.3% at two months after Dose 2 of HRV vaccine or placebo and from 70.1% to 80.1% at the end of the first efficacy follow-up period.

Antibody responses to all routine vaccine antigens at two months after Dose 2 of HRV vaccine or placebo in the three HRV vaccine groups were similar to those of the placebo (control) indicating that there appeared to be no impact of HRV vaccine on immunogenicity of OPV and concomitantly administered DTPw-HB+Hib vaccine, except for anti-diphtheria antibodies. There was a trend towards lower anti-diphtheria antibody seroprotection rates in the $10^{4.7}$ ffu and $10^{5.2}$ ffu HRV vaccine groups as compared to the placebo group at two months after Dose 2 of HRV vaccine or placebo, but rates were similar at the end of the first efficacy follow-up period.

Persistence data for antibodies to all routine vaccine antigens at end of the first efficacy follow-up period in the three HRV vaccine groups were similar to those of the placebo (control) indicating that there was no apparent effect of the HRV vaccine on the immunogenicity of routine vaccines after completion of the three-dose primary vaccination course.

Antibody responses to each of the routine vaccine antigens at each timepoint are presented hereafter. Results of exploratory inferential analysis for differences between each vaccine group and placebo and between the pooled HRV vaccine group and the placebo group with respect to immune response to concomitant vaccination at two months after Dose 2 of HRV vaccine or placebo and at the end of first efficacy follow up period are also presented. Conclusions can not be drawn from the inferential analyses since clinical limits for non-inferiority were not pre-defined.

Anti-diphtheria antibody response

Anti-diphtheria antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 36.

Table 36: Anti-diphtheria antibody GMCs and seroprotection rates (ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 0.1 IU/ml				GMC (IU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	146	94	64.4	56.0	72.1	0.204	0.164	0.253
	PII(M10)	164	115	70.1	62.5	77.0	0.189	0.161	0.223
HRV $10^{5.2}$	PII(M4)	136	80	58.8	50.1	67.2	0.183	0.146	0.230
	PII(M10)	149	102	68.5	60.3	75.8	0.186	0.156	0.221
HRV $10^{5.8}$	PII(M4)	130	98	75.4	67.1	82.5	0.247	0.199	0.307
	PII(M10)	142	100	70.4	62.2	77.8	0.188	0.157	0.224
Pooled HRV groups	PII(M4)	412	272	66.0	61.2	70.6	0.209	0.184	0.237
	PII(M10)	455	317	69.7	65.2	73.9	0.188	0.170	0.207
Placebo	PII(M4)	133	94	70.7	62.2	78.2	0.276	0.216	0.354
	PII(M10)	149	111	74.5	66.7	81.3	0.201	0.169	0.238

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

Supplement 113 and Supplement 114 respectively present the standardized asymptotic 95% CIs for the difference in anti-diphtheria antibody seroprotection rate between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 115 and Supplement 116 respectively present the 95% CIs for the ratio of anti-diphtheria antibody GMCs between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 117 and Supplement 118 respectively present reverse cumulative distribution curves of anti-diphtheria antibody concentrations two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Anti-tetanus antibody response

Anti-tetanus antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 37.

Table 37: Anti-tetanus antibody GMCs and seroprotection rates (ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 0.1 IU/ml				GMC (IU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	147	145	98.6	95.2	99.8	1.106	0.925	1.321
	PII(M10)	166	166	100	97.8	100.0	1.230	1.106	1.368
HRV $10^{5.2}$	PII(M4)	136	136	100	97.3	100.0	1.096	0.921	1.305
	PII(M10)	150	148	98.7	95.3	99.8	1.140	1.008	1.290
HRV $10^{5.8}$	PII(M4)	131	128	97.7	93.5	99.5	1.051	0.868	1.274
	PII(M10)	143	143	100	97.5	100.0	1.179	1.040	1.337
Pooled HRV groups	PII(M4)	414	409	98.8	97.2	99.6	1.085	0.978	1.204
	PII(M10)	459	457	99.6	98.4	99.9	1.184	1.107	1.267
Placebo	PII(M4)	134	133	99.3	95.9	100.0	1.160	0.960	1.403
	PII(M10)	149	149	100	97.6	100.0	1.121	0.992	1.266

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

Supplement 119 and Supplement 120 respectively present the standardized asymptotic 95% CIs for the difference in anti-tetanus antibody seroprotection rate between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 121 and Supplement 122 respectively present the 95% CIs for the ratio of anti-tetanus antibody GMCs between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 123 and Supplement 124 respectively present reverse cumulative distribution curves of anti-tetanus antibody concentrations two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Anti-BPT antibody response

Anti-BPT antibody GMCs and seropositivity rates at each sampling timepoint are presented in Table 38.

Table 38: Anti-BPT antibody GMCs and seropositivity rates (ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 15 EL.U/ml				GMC (EL.U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	144	94	65.3	56.9	73.0	19.4	17.0	22.2
	PII(M10)	165	124	75.2	67.8	81.5	22.5	20.1	25.2
HRV $10^{5.2}$	PII(M4)	134	79	59.0	50.1	67.4	18.5	16.0	21.3
	PII(M10)	151	121	80.1	72.9	86.2	25.2	22.1	28.7
HRV $10^{5.8}$	PII(M4)	131	84	64.1	55.3	72.3	18.4	16.1	21.0
	PII(M10)	144	101	70.1	62.0	77.5	22.2	19.3	25.5
Pooled HRV groups	PII(M4)	409	257	62.8	58.0	67.5	18.8	17.4	20.3
	PII(M10)	460	346	75.2	71.0	79.1	23.2	21.6	25.0
Placebo	PII(M4)	130	80	61.5	52.6	69.9	17.6	15.4	20.2
	PII(M10)	148	106	71.6	63.6	78.7	22.4	19.4	25.7

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered seropositivity level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

Supplement 125 and Supplement 126 respectively present the standardized asymptotic 95% CIs for the difference in anti-BPT antibody seropositivity rate between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 127 and Supplement 128 respectively present the 95% CIs for the ratio of anti-BPT antibody GMCs between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 129 and Supplement 130 respectively present reverse cumulative distribution curves of anti-BPT antibody concentrations two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Anti-HBs antibody response

Anti-HBs antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 39.

Table 39: Anti-HBs antibody GMCs and seroprotection rates (ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 10 mIU/ml				GMC (mIU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	147	145	98.6	95.2	99.8	550.607	447.434	677.569
	PII(M10)	165	157	95.2	90.7	97.9	212.673	171.244	264.126
HRV $10^{5.2}$	PII(M4)	136	134	98.5	94.8	99.8	595.706	470.668	753.960
	PII(M10)	150	145	96.7	92.4	98.9	214.367	174.033	264.050
HRV $10^{5.8}$	PII(M4)	134	130	97.0	92.5	99.2	515.918	407.055	653.895
	PII(M10)	143	140	97.9	94.0	99.6	199.973	162.194	246.553
Pooled HRV groups	PII(M4)	417	409	98.1	96.3	99.2	553.237	485.976	629.806
	PII(M10)	458	442	96.5	94.4	98.0	209.166	185.198	236.237
Placebo	PII(M4)	133	131	98.5	94.7	99.8	674.888	527.372	863.667
	PII(M10)	149	144	96.6	92.3	98.9	238.668	193.571	294.271

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

Supplement 131 and Supplement 132 respectively present the standardized asymptotic 95% CIs for the difference in anti-HBs antibody seroprotection rate between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 133 and Supplement 134 respectively present the 95% CIs for the ratio of anti-HBs antibody GMCs between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 135 and Supplement 136 respectively present reverse cumulative distribution curves of anti-HBs antibody concentrations two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Anti-PRP antibody response

Anti-PRP antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 40.

Table 40: Anti-PRP antibody GMCs and seroprotection rates (ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 0.15 mcg/ml				≥ 1 mcg/ml				GMC (mcg/ml)		
					95% CI		n	%	95% CI		Value	95% CI	
			n	%	LL	UL			LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	143	143	100	97.5	100	138	96.5	92.0	98.9	6.420	5.359	7.691
	PII(M10)	165	164	99.4	96.7	100	155	93.9	89.1	97.1	3.987	3.477	4.571
HRV $10^{5.2}$	PII(M4)	136	135	99.3	96.0	100	120	88.2	81.6	93.1	5.638	4.491	7.078
	PII(M10)	149	148	99.3	96.3	100	136	91.3	85.5	95.3	3.995	3.419	4.667
HRV $10^{5.8}$	PII(M4)	133	132	99.2	95.9	100	121	91.0	84.8	95.3	5.114	4.158	6.288
	PII(M10)	143	143	100	97.5	100	131	91.6	85.8	95.6	3.592	3.107	4.152
Pooled HRV groups	PII(M4)	412	410	99.5	98.3	99.9	379	92.0	88.9	94.4	5.715	5.080	6.429
	PII(M10)	457	455	99.6	98.4	99.9	422	92.3	89.5	94.6	3.861	3.552	4.198
Placebo	PII(M4)	131	130	99.2	95.8	100	117	89.3	82.7	94.0	5.083	4.072	6.344
	PII(M10)	149	149	100	97.6	100	141	94.6	89.7	97.7	3.842	3.314	4.454

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

Supplement 137 to Supplement 140 present the standardized asymptotic 95% CIs for the difference in anti-PRP antibody seroprotection rates (≥ 0.15 mcg/ml and ≥ 1 mcg/ml) between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 141 and Supplement 142 respectively present the 95% CIs for the ratio of anti-PRP antibody GMCs between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 143 and Supplement 144 respectively present reverse cumulative distribution curves of anti-PRP antibody concentrations two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Anti-poliovirus types 1, 2 and 3 antibody response

Anti-poliovirus types 1, 2 and 3 antibody GMTs and seroprotection rates at each sampling timepoint are presented in Table 41.

Table 41: Anti-poliovirus types 1, 2 and 3 antibody GMTs and seroprotection rates (ATP cohort for immunogenicity analysis)

Antibody	Group	Timing	N	≥ 1:8 dilution				GMT		
						95% CI		Value	95% CI	
				n	%	LL	UL		LL	UL
Anti-polio type 1	HRV $10^{4.7}$	PII(M4)	147	145	98.6	95.2	99.8	1546.9	1207.7	1981.3
		PII(M10)	156	155	99.4	96.5	100	802.1	662.2	971.7
	HRV $10^{5.2}$	PII(M4)	135	132	97.8	93.6	99.5	1120.1	852.6	1471.6
		PII(M10)	139	139	100	97.4	100	731.3	603.3	886.5
	HRV $10^{5.8}$	PII(M4)	133	131	98.5	94.7	99.8	1261.4	979.9	1623.7
		PII(M10)	134	134	100	97.3	100	714.8	574.8	889.0
	Pooled HRV groups	PII(M4)	415	408	98.3	96.6	99.3	1304.5	1125.0	1512.7
		PII(M10)	429	428	99.8	98.7	100	751.0	669.5	842.4
	Placebo	PII(M4)	130	129	99.2	95.8	100	1322.7	1039.4	1683.0
		PII(M10)	138	138	100	97.4	100	693.9	566.9	849.3
Anti-polio type 2	HRV $10^{4.7}$	PII(M4)	147	145	98.6	95.2	99.8	1138.6	913.3	1419.4
		PII(M10)	164	162	98.8	95.7	99.9	469.7	390.1	565.5
	HRV $10^{5.2}$	PII(M4)	135	134	99.3	95.9	100	1042.7	838.3	1297.0
		PII(M10)	147	147	100	97.5	100	472.6	404.9	551.5
	HRV $10^{5.8}$	PII(M4)	133	132	99.2	95.9	100	1346.2	1101.4	1645.3
		PII(M10)	140	140	100	97.4	100	523.6	445.3	615.7
	Pooled HRV groups	PII(M4)	415	411	99.0	97.6	99.7	1167.5	1032.4	1320.3
		PII(M10)	451	449	99.6	98.4	99.9	486.8	441.6	536.6
	Placebo	PII(M4)	130	129	99.2	95.8	100	1112.1	892.9	1385.1
		PII(M10)	148	147	99.3	96.3	100	438.7	372.5	516.6
Anti-polio type 3	HRV $10^{4.7}$	PII(M4)	147	128	87.1	80.6	92.0	184.1	137.9	245.7
		PII(M10)	164	151	92.1	86.8	95.7	131.1	105.6	162.7
	HRV $10^{5.2}$	PII(M4)	135	114	84.4	77.2	90.1	158.0	113.8	219.3
		PII(M10)	147	134	91.2	85.4	95.2	107.3	83.7	137.6
	HRV $10^{5.8}$	PII(M4)	133	119	89.5	83.0	94.1	181.1	135.2	242.5
		PII(M10)	140	133	95.0	90.0	98.0	130.9	104.8	163.5
	Pooled HRV groups	PII(M4)	415	361	87.0	83.4	90.1	174.2	146.5	207.2
		PII(M10)	451	418	92.7	89.9	94.9	122.8	107.6	140.0
	Placebo	PII(M4)	130	110	84.6	77.2	90.3	155.5	110.7	218.4
		PII(M10)	148	138	93.2	87.9	96.7	109.2	87.6	136.2

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with titer above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

Supplement 145 to Supplement 150 present the standardized asymptotic 95% CIs for the difference in anti-poliovirus types 1, 2 and 3 antibody seroprotection rates between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the efficacy follow-up period.

Supplement 151 to Supplement 156 respectively present the 95% CIs for the ratio of anti-poliovirus types 1, 2 and 3 antibody GMTs between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 157 to Supplement 162 present reverse cumulative distribution curves of anti-poliovirus types 1, 2 and 3 antibody titers two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

7.3 Total vaccinated cohort for immunogenicity analysis

The total vaccinated cohort for immunogenicity analysis (subjects with serology results available) consisted of 2151 subjects (537 subjects in the $10^{4.7}$ ffu HRV vaccine group, 535 subjects in the $10^{5.2}$ ffu HRV vaccine group, 540 subjects in the $10^{5.8}$ ffu HRV vaccine group and 539 subjects the placebo group).

Supplement 105 to Supplement 112 present immunogenicity of the HRV vaccine for the total vaccinated cohort.

Supplement 163 to Supplement 167 present immunogenicity of the routine vaccinations for the total vaccinated cohort.

The results of the total vaccinated cohort analyses were consistent with those observed in the ATP cohort.

8 Exploratory evaluation of three doses of HRV vaccine or placebo

Due to the small number of subjects who received a third dose of HRV vaccine or placebo, the results obtained in this exploratory evaluation should be interpreted with caution.

8.1 Study population receiving three doses of HRV vaccine or placebo

8.1.1 Study dates

The first visit for the first subject enrolled as part of the subset receiving three doses of HRV vaccine or placebo took place on January 17, 2002. The data lock point for this final analysis was April 8, 2003 (the day on which the last subject completed the study visit at the end of the first efficacy follow-up period).

8.2 Subject eligibility and attrition from study

8.2.1 Number and distribution of subjects

All of the 121 subjects who comprised the subset to receive three doses of HRV vaccine or placebo were enrolled in Brazil.

8.2.2 Study completion and drop out

There were no drop outs until the end of the first efficacy follow-up period among the subset receiving three doses of HRV vaccine or placebo.

8.2.3 Eligibility for analysis

Exploratory analyses for the subset receiving three doses of HRV vaccine or placebo were performed only on the total vaccinated cohort. All of the 121 subjects enrolled to receive three doses of HRV vaccine or placebo were included in the total vaccinated cohort.

8.2.4 Compliance with protocol specified procedures

Written informed consent was obtained from parents/guardians of all subjects prior to entry in the study.

All subjects receiving three doses of HRV vaccine or placebo returned for the study visit at the end of the first efficacy follow-up period. Therefore compliance with study completion until end of the first efficacy follow-up period was 100%.

Compliance for reactogenicity reporting was 100%.

Regurgitation within 30 minutes was reported following 30 doses. None of these subjects were eliminated from analyses since only total vaccinated cohort analyses were performed for the subset receiving three doses of HRV vaccine or placebo.

Compliance for administration of routine DTPw-HB+Hib vaccine in the subset receiving three doses of HRV vaccine or placebo was as follows:

- In the total vaccinated cohort, all subjects received the DTPw-HB+Hib vaccine concomitantly with the first (except one in the HRV $10^{4.7}$ group), second and third doses of HRV vaccine or placebo. None of the subjects received OPV concomitantly with the first, second and third doses of HRV vaccine or placebo.

- In the total vaccinated cohort for subjects with available routine vaccination serology results at Visit 3, more than 90% of subjects in each group received two doses of DTPw-HB+Hib and OPV vaccines between Visit 1 and before Visit 3.
- In the total vaccinated cohort for subjects with available routine vaccination serology results at Visit 4, more than 96% of subjects in each group received three doses of DTPw-HB+Hib and OPV vaccines between Visit 1 and before the end of the first efficacy follow-up period.

8.3 Demographic characteristics of the total vaccinated cohort

Demographic characteristics for the total vaccinated cohort are summarized in Supplement 168. The mean age at the time of Dose 1 of HRV vaccine or placebo was 9.8 weeks (range 6–12 weeks). The mean age at the time of Dose 2 of HRV vaccine or placebo was 19.5 weeks (range 15–25 weeks). The mean age at the time of Dose 3 of HRV vaccine or placebo was 29.3 weeks (range 24–37 weeks). The demographic profile of the four groups was similar with respect to mean age, mean height and mean weight at the time of Dose 1 of HRV vaccine or placebo and race distribution. Observed differences in female to male ratio between the groups can be attributed to random chance and are not deemed clinically relevant.

It should be noted that subjects in the cohort receiving three doses of HRV vaccine or placebo were older than those in the cohort planned to receive two doses of HRV vaccine or placebo (See Section 4.3.1).

Supplement 169 presents the weight and height increases from Visit 1 to each of the subsequent visits by group. The mean increase in height and weight from Visit 1 to Visits 2, 3 and 4 was similar among the four groups.

Supplement 170 presents a summary of feeding criteria on the day of each study vaccination by group. The feeding profile (percentage of subjects who were fed with breast milk, infant formula or both) of the four groups was similar.

8.4 Exploratory analysis of efficacy

8.4.1 Data sets analyzed

Exploratory analysis of efficacy was performed only on the total vaccinated cohort. See Section 3.15.4 for definition of cohorts identified for analyses.

8.4.2 Total vaccinated cohort for efficacy analysis

The total vaccinated cohort for analysis of efficacy consisted of 121 subjects (31 subjects in the $10^{4.7}$ ffu HRV vaccine group, 30 subjects in the $10^{5.2}$ ffu HRV vaccine group, 30 subjects in the $10^{5.8}$ ffu HRV vaccine group and 30 subjects the placebo group).

8.4.2.1 Characterization of GE episodes reported during the first efficacy follow-up period

The first efficacy follow-up period started from two weeks after Dose 3 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age).

Table 42 presents the number and percentage of subjects who reported RV GE of any intensity during the first efficacy follow-up period. Table 43 presents the number and percentage of subjects who reported RV GE of severe intensity during the first efficacy follow-up period.

As seen from Table 42 and Table 43, the percentages of subjects reporting RV GE was lower in the pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group. None of the subjects in the HRV vaccine groups reported severe RV GE while all RV GE cases in the placebo group were rated as severe.

Table 42: Percentage of subjects reporting any RV GE from 2 weeks after Dose 3 of HRV vaccine or placebo until end of the first efficacy follow-up period (total vaccinated cohort for efficacy analysis)

			n/N		
				95%CI	
Group	**N**	**n**	**%**	**LL**	**UL**
HRV $10^{4.7}$	31	1	3.2	0.1	16.7
HRV $10^{5.2}$	30	0	0.0	0.0	11.6
HRV $10^{5.8}$	30	0	0.0	0.0	11.6
Pooled HRV Groups	91	1	1.1	0.0	6.0
Placebo	30	5	16.7	5.6	34.7

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
% = percentage of subjects reporting at least one RV GE episode in each group
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 43: Percentage of subjects reporting severe RV GE from 2 weeks after Dose 3 of HRV vaccine or placebo until end of the first efficacy follow-up period (total vaccinated cohort for efficacy analysis)

			n/N		
				95%CI	
Group	**N**	**n**	**%**	**LL**	**UL**
HRV $10^{4.7}$	31	0	0.0	0.0	11.2
HRV $10^{5.2}$	30	0	0.0	0.0	11.6
HRV $10^{5.8}$	30	0	0.0	0.0	11.6
Pooled HRV Groups	91	0	0.0	0.0	4.0
Placebo	30	5	16.7	5.6	34.7

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

No concurrent pathogens were identified in RV GE cases occurring from two weeks after Dose 3 of HRV vaccine or placebo until the end of the efficacy follow-up period.

8.5 Analysis of safety

8.5.1 Data sets analyzed

Analysis of safety was performed only on the total vaccinated cohort. See Section 3.15.4 for description of analyses cohorts.

8.5.2 Total vaccinated cohort for safety analysis

The total vaccinated cohort for analysis of safety consisted of 121 subjects (31 subjects in the $10^{4.7}$ ffu HRV vaccine group, 30 subjects in the $10^{5.2}$ ffu HRV vaccine group, 30 subjects in the $10^{5.8}$ ffu HRV vaccine group and 30 subjects the placebo group).

All subjects who were planned to receive a third dose of HRV vaccine or placebo, received their three doses.

8.5.2.1 Overall incidence of symptoms

Table 44 presents the percentages of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15-day solicited follow-up period for all doses.

The incidences of symptoms (solicited or unsolicited) during the 15-day solicited follow-up period were high in all groups. All subjects reported symptoms (solicited or unsolicited) during the 15-day solicited follow-up period after Dose 1 of HRV vaccine or placebo. Incidences of symptoms (solicited or unsolicited) including those rated as grade "3" in intensity and those assessed as related to vaccination were similar between the groups.

Table 44: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15-day solicited follow-up period (total vaccinated cohort for safety analysis)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	HRV $10^{4.7}$	31	31	100	88.8	100
	HRV $10^{5.2}$	30	30	100	88.4	100
	HRV $10^{5.8}$	30	30	100	88.4	100
	Pooled HRV groups	91	91	100	96.0	100
	Placebo	30	30	100	88.4	100
Dose 2	HRV $10^{4.7}$	31	28	90.3	74.2	98.0
	HRV $10^{5.2}$	30	28	93.3	77.9	99.2
	HRV $10^{5.8}$	30	29	96.7	82.8	99.9
	Pooled HRV groups	91	85	93.4	86.2	97.5
	Placebo	30	29	96.7	82.8	99.9
Dose 3	HRV $10^{4.7}$	31	30	96.8	83.3	99.9
	HRV $10^{5.2}$	30	29	96.7	82.8	99.9
	HRV $10^{5.8}$	30	29	96.7	82.8	99.9
	Pooled HRV groups	91	88	96.7	90.7	99.3
	Placebo	30	28	93.3	77.9	99.2
Overall/dose	HRV $10^{4.7}$	93	89	95.7	89.4	98.8
	HRV $10^{5.2}$	90	87	96.7	90.6	99.3
	HRV $10^{5.8}$	90	88	97.8	92.2	99.7
	Pooled HRV groups	273	264	96.7	93.8	98.5
	Placebo	90	87	96.7	90.6	99.3
Overall/subject	HRV $10^{4.7}$	31	31	100	88.8	100
	HRV $10^{5.2}$	30	30	100	88.4	100
	HRV $10^{5.8}$	30	30	100	88.4	100
	Pooled HRV groups	91	91	100	96.0	100
	Placebo	30	30	100	88.4	100

Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For each dose:
N = number of subjects having received the considered dose of HRV vaccine or placebo
n/% = number/percentage of subjects reporting at least one symptom for the considered dose of HRV vaccine or placebo
For overall/dose:
N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject:
N= number of subjects having received at least one dose of HRV vaccine or placebo
n/%= number percentage of subjects reporting at least one symptom

Supplement 171 and Supplement 172 respectively present the percentage of doses and of subjects reporting grade "3" and related symptoms (solicited or unsolicited) during the 15-day solicited follow-up period.

8.5.2.2 Solicited signs and symptoms

Table 45, Table 46 and Table 47 present the percentage of subjects with specific solicited symptoms including those graded "2 or 3" in intensity, those graded "3" in intensity and those considered to be related to vaccination, during the 15-day solicited follow-up period after each dose of HRV vaccine or placebo.

Supplement 173 presents the percentage of doses and subjects reporting specific solicited symptoms including those graded "2 or 3" in intensity, those graded "3" in intensity and those considered to be related to vaccination, during the 15-day solicited follow-up period after any dose of HRV vaccine or placebo.

Cough/runny nose, fever and irritability were the most commonly reported solicited symptoms in all groups. Diarrhea was the least frequently reported solicited general symptom. Incidences were similar between the groups for each solicited symptom including those rated as grade "2 or 3" in intensity, those rated as grade "3" in intensity and those assessed as related to vaccination.

An additional dose of HRV vaccine or placebo or the higher age of the subjects in this cohort did not appear to impact on the reactogenicity profile of the HRV vaccine as compared to the placebo.

*Table 45: Percentage of subjects with each solicited symptom including those graded "2 or 3", those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after **Dose 1** of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Group		HRV $10^{4.7}$ N = 31				HRV $10^{5.2}$ N = 30				HRV $10^{5.8}$ N = 30			
		n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL
Cough/ runny nose	Total	18	58.1	39.1	75.5	22	73.3	54.1	87.7	21	70.0	50.6	85.3
	Grade 2 or 3	5	16.1	5.5	33.7	8	26.7	12.3	45.9	11	36.7	19.9	56.1
	Grade 3	1	3.2	0.1	16.7	1	3.3	0.1	17.2	3	10.0	2.1	26.5
	Related	12	38.7	21.8	57.8	16	53.3	34.3	71.7	8	26.7	12.3	45.9
Diarrhea	Total	7	22.6	9.6	41.1	6	20.0	7.7	38.6	7	23.3	9.9	42.3
	Grade 2 or 3	5	16.1	5.5	33.7	2	6.7	0.8	22.1	4	13.3	3.8	30.7
	Grade 3	3	9.7	2.0	25.8	0	0.0	0.0	11.6	0	0.0	0.0	11.6
	Related	6	19.4	7.5	37.5	5	16.7	5.6	34.7	4	13.3	3.8	30.7
Irritability/ fussiness	Total	28	90.3	74.2	98.0	27	90.0	73.5	97.9	27	90.0	73.5	97.9
	Grade 2 or 3	19	61.3	42.2	78.2	20	66.7	47.2	82.7	20	66.7	47.2	82.7
	Grade 3	3	9.7	2.0	25.8	4	13.3	3.8	30.7	2	6.7	0.8	22.1
	Related	26	83.9	66.3	94.5	26	86.7	69.3	96.2	26	86.7	69.3	96.2
Loss of appetite	Total	6	19.4	7.5	37.5	9	30.0	14.7	49.4	7	23.3	9.9	42.3
	Grade 2 or 3	3	9.7	2.0	25.8	2	6.7	0.8	22.1	1	3.3	0.1	17.2
	Grade 3	0	0.0	0.0	11.2	0	0.0	0.0	11.6	0	0.0	0.0	11.6
	Related	2	6.5	0.8	21.4	7	23.3	9.9	42.3	7	23.3	9.9	42.3
Fever	Total	24	77.4	58.9	90.4	21	70.0	50.6	85.3	23	76.7	57.7	90.1
	Grade 2 or 3	7	22.6	9.6	41.1	10	33.3	17.3	52.8	10	33.3	17.3	52.8
	Grade 3	1	3.2	0.1	16.7	0	0.0	0.0	11.6	0	0.0	0.0	11.6
	Related	23	74.2	55.4	88.1	18	60.0	40.6	77.3	22	73.3	54.1	87.7
Vomiting	Total	7	22.6	9.6	41.1	12	40.0	22.7	59.4	7	23.3	9.9	42.3
	Grade 2 or 3	4	12.9	3.6	29.8	6	20.0	7.7	38.6	2	6.7	0.8	22.1
	Grade 3	2	6.5	0.8	21.4	2	6.7	0.8	22.1	0	0.0	0.0	11.6
	Related	5	16.1	5.5	33.7	11	36.7	19.9	56.1	5	16.7	5.6	34.7

Notes: N = number of subjects having received Dose 1 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 1 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

*Table 45 (continued): Percentage of subjects with each solicited symptom including those graded "2 or 3", those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after **Dose 1** of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Group		**Pooled HRV groups N = 91**				**Placebo N = 30**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
Cough/ runny nose	Total	61	67.0	56.4	76.5	23	76.7	57.7	90.1
	Grade 2 or 3	24	26.4	17.7	36.7	11	36.7	19.9	56.1
	Grade 3	5	5.5	1.8	12.4	1	3.3	0.1	17.2
	Related	36	39.6	29.5	50.4	11	36.7	19.9	56.1
Diarrhea	Total	20	22.0	14.0	31.9	4	13.3	3.8	30.7
	Grade 2 or 3	11	12.1	6.2	20.6	3	10.0	2.1	26.5
	Grade 3	3	3.3	0.7	9.3	1	3.3	0.1	17.2
	Related	15	16.5	9.5	25.7	3	10.0	2.1	26.5
Irritability/ fussiness	Total	82	90.1	82.1	95.4	25	83.3	65.3	94.4
	Grade 2 or 3	59	64.8	54.1	74.6	18	60.0	40.6	77.3
	Grade 3	9	9.9	4.6	17.9	5	16.7	5.6	34.7
	Related	78	85.7	76.8	92.2	22	73.3	54.1	87.7
Loss of appetite	Total	22	24.2	15.8	34.3	12	40.0	22.7	59.4
	Grade 2 or 3	6	6.6	2.5	13.8	8	26.7	12.3	45.9
	Grade 3	0	0.0	0.0	4.0	0	0.0	0.0	11.6
	Related	16	17.6	10.4	27.0	10	33.3	17.3	52.8
Fever	Total	68	74.7	64.5	83.3	18	60.0	40.6	77.3
	Grade 2 or 3	27	29.7	20.5	40.2	5	16.7	5.6	34.7
	Grade 3	1	1.1	0.0	6.0	0	0.0	0.0	11.6
	Related	63	69.2	58.7	78.5	16	53.3	34.3	71.7
Vomiting	Total	26	28.6	19.6	39.0	8	26.7	12.3	45.9
	Grade 2 or 3	12	13.2	7.0	21.9	6	20.0	7.7	38.6
	Grade 3	4	4.4	1.2	10.9	1	3.3	0.1	17.2
	Related	21	23.1	14.9	33.1	4	13.3	3.8	30.7

Notes: N = number of subjects having received Dose 1 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 1 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

*Table 46: Percentage of subjects with each solicited symptom including those graded "2 or 3", those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after **Dose 2** of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Group		HRV $10^{4.7}$ N = 31				HRV $10^{5.2}$ N = 30				HRV $10^{5.8}$ N = 30			
		n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL
Cough/ runny nose	Total	22	71.0	52.0	85.8	25	83.3	65.3	94.4	27	90.0	73.5	97.9
	Grade 2 or 3	14	45.2	27.3	64.0	17	56.7	37.4	74.5	14	46.7	28.3	65.7
	Grade 3	4	12.9	3.6	29.8	7	23.3	9.9	42.3	1	3.3	0.1	17.2
	Related	8	25.8	11.9	44.6	8	26.7	12.3	45.9	14	46.7	28.3	65.7
Diarrhea	Total	3	9.7	2.0	25.8	2	6.7	0.8	22.1	5	16.7	5.6	34.7
	Grade 2 or 3	1	3.2	0.1	16.7	1	3.3	0.1	17.2	4	13.3	3.8	30.7
	Grade 3	0	0.0	0.0	11.2	0	0.0	0.0	11.6	0	0.0	0.0	11.6
	Related	2	6.5	0.8	21.4	2	6.7	0.8	22.1	4	13.3	3.8	30.7
Irritability/ fussiness	Total	18	58.1	39.1	75.5	17	56.7	37.4	74.5	15	50.0	31.3	68.7
	Grade 2 or 3	11	35.5	19.2	54.6	12	40.0	22.7	59.4	10	33.3	17.3	52.8
	Grade 3	3	9.7	2.0	25.8	2	6.7	0.8	22.1	2	6.7	0.8	22.1
	Related	17	54.8	36.0	72.7	15	50.0	31.3	68.7	14	46.7	28.3	65.7
Loss of appetite	Total	13	41.9	24.5	60.9	10	33.3	17.3	52.8	7	23.3	9.9	42.3
	Grade 2 or 3	2	6.5	0.8	21.4	5	16.7	5.6	34.7	4	13.3	3.8	30.7
	Grade 3	0	0.0	0.0	11.2	1	3.3	0.1	17.2	1	3.3	0.1	17.2
	Related	7	22.6	9.6	41.1	7	23.3	9.9	42.3	7	23.3	9.9	42.3
Fever	Total	20	64.5	45.4	80.8	13	43.3	25.5	62.6	15	50.0	31.3	68.7
	Grade 2 or 3	13	41.9	24.5	60.9	8	26.7	12.3	45.9	7	23.3	9.9	42.3
	Grade 3	2	6.5	0.8	21.4	2	6.7	0.8	22.1	1	3.3	0.1	17.2
	Related	20	64.5	45.4	80.8	12	40.0	22.7	59.4	13	43.3	25.5	62.6
Vomiting	Total	12	38.7	21.8	57.8	7	23.3	9.9	42.3	11	36.7	19.9	56.1
	Grade 2 or 3	5	16.1	5.5	33.7	4	13.3	3.8	30.7	5	16.7	5.6	34.7
	Grade 3	2	6.5	0.8	21.4	1	3.3	0.1	17.2	2	6.7	0.8	22.1
	Related	6	19.4	7.5	37.5	5	16.7	5.6	34.7	6	20.0	7.7	38.6

Notes: N = number of subjects having received Dose 2 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 2 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

*Table 46 (continued): Percentage of subjects with each solicited symptom including those graded "2 or 3", those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after **Dose 2** of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Group		**Pooled HRV groups N = 91**				**Placebo N = 30**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
Cough/ runny nose	Total	74	81.3	71.8	88.7	23	76.7	57.7	90.1
	Grade 2 or 3	45	49.5	38.8	60.1	13	43.3	25.5	62.6
	Grade 3	12	13.2	7.0	21.9	3	10.0	2.1	26.5
	Related	30	33.0	23.5	43.6	14	46.7	28.3	65.7
Diarrhea	Total	10	11.0	5.4	19.3	7	23.3	9.9	42.3
	Grade 2 or 3	6	6.6	2.5	13.8	3	10.0	2.1	26.5
	Grade 3	0	0.0	0.0	4.0	1	3.3	0.1	17.2
	Related	8	8.8	3.9	16.6	6	20.0	7.7	38.6
Irritability/ fussiness	Total	50	54.9	44.2	65.4	17	56.7	37.4	74.5
	Grade 2 or 3	33	36.3	26.4	47.0	10	33.3	17.3	52.8
	Grade 3	7	7.7	3.1	15.2	1	3.3	0.1	17.2
	Related	46	50.5	39.9	61.2	15	50.0	31.3	68.7
Loss of appetite	Total	30	33.0	23.5	43.6	6	20.0	7.7	38.6
	Grade 2 or 3	11	12.1	6.2	20.6	3	10.0	2.1	26.5
	Grade 3	2	2.2	0.3	7.7	0	0.0	0.0	11.6
	Related	21	23.1	14.9	33.1	5	16.7	5.6	34.7
Fever	Total	48	52.7	42.0	63.3	11	36.7	19.9	56.1
	Grade 2 or 3	28	30.8	21.5	41.3	4	13.3	3.8	30.7
	Grade 3	5	5.5	1.8	12.4	0	0.0	0.0	11.6
	Related	45	49.5	38.8	60.1	9	30.0	14.7	49.4
Vomiting	Total	30	33.0	23.5	43.6	4	13.3	3.8	30.7
	Grade 2 or 3	14	15.4	8.7	24.5	1	3.3	0.1	17.2
	Grade 3	5	5.5	1.8	12.4	0	0.0	0.0	11.6
	Related	17	18.7	11.3	28.2	4	13.3	3.8	30.7

Notes: N = number of subjects having received Dose 2 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 2 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

*Table 47: Percentage of subjects with each solicited symptom including those graded "2 or 3", those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after **Dose 3** of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Group		HRV $10^{4.7}$ N = 31				HRV $10^{5.2}$ N = 30				HRV $10^{5.8}$ N = 30			
		n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL
Cough/ runny nose	Total	24	77.4	58.9	90.4	25	83.3	65.3	94.4	24	80.0	61.4	92.3
	Grade 2 or 3	12	38.7	21.8	57.8	11	36.7	19.9	56.1	12	40.0	22.7	59.4
	Grade 3	3	9.7	2.0	25.8	4	13.3	3.8	30.7	2	6.7	0.8	22.1
	Related	10	32.3	16.7	51.4	9	30.0	14.7	49.4	11	36.7	19.9	56.1
Diarrhea	Total	6	19.4	7.5	37.5	3	10.0	2.1	26.5	7	23.3	9.9	42.3
	Grade 2 or 3	5	16.1	5.5	33.7	1	3.3	0.1	17.2	6	20.0	7.7	38.6
	Grade 3	4	12.9	3.6	29.8	1	3.3	0.1	17.2	3	10.0	2.1	26.5
	Related	4	12.9	3.6	29.8	1	3.3	0.1	17.2	6	20.0	7.7	38.6
Irritability/ fussiness	Total	17	54.8	36.0	72.7	13	43.3	25.5	62.6	19	63.3	43.9	80.1
	Grade 2 or 3	8	25.8	11.9	44.6	8	26.7	12.3	45.9	8	26.7	12.3	45.9
	Grade 3	3	9.7	2.0	25.8	1	3.3	0.1	17.2	2	6.7	0.8	22.1
	Related	16	51.6	33.1	69.8	10	33.3	17.3	52.8	16	53.3	34.3	71.7
Loss of appetite	Total	12	38.7	21.8	57.8	11	36.7	19.9	56.1	14	46.7	28.3	65.7
	Grade 2 or 3	7	22.6	9.6	41.1	5	16.7	5.6	34.7	6	20.0	7.7	38.6
	Grade 3	2	6.5	0.8	21.4	1	3.3	0.1	17.2	1	3.3	0.1	17.2
	Related	11	35.5	19.2	54.6	8	26.7	12.3	45.9	12	40.0	22.7	59.4
Fever	Total	17	54.8	36.0	72.7	15	50.0	31.3	68.7	14	46.7	28.3	65.7
	Grade 2 or 3	8	25.8	11.9	44.6	4	13.3	3.8	30.7	8	26.7	12.3	45.9
	Grade 3	0	0.0	0.0	11.2	0	0.0	0.0	11.6	2	6.7	0.8	22.1
	Related	15	48.4	30.2	66.9	13	43.3	25.5	62.6	13	43.3	25.5	62.6
Vomiting	Total	9	29.0	14.2	48.0	9	30.0	14.7	49.4	7	23.3	9.9	42.3
	Grade 2 or 3	5	16.1	5.5	33.7	4	13.3	3.8	30.7	3	10.0	2.1	26.5
	Grade 3	1	3.2	0.1	16.7	1	3.3	0.1	17.2	1	3.3	0.1	17.2
	Related	9	29.0	14.2	48.0	7	23.3	9.9	42.3	6	20.0	7.7	38.6

Notes: N = number of subjects having received Dose 3 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 3 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

*Table 47 (continued): Percentage of subjects with each solicited symptom including those graded "2 or 3", those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after **Dose 3** of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Group		**Pooled HRV groups N = 91**				**Placebo N = 30**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
Cough/ runny nose	Total	73	80.2	70.6	87.8	18	60.0	40.6	77.3
	Grade 2 or 3	35	38.5	28.4	49.2	10	33.3	17.3	52.8
	Grade 3	9	9.9	4.6	17.9	2	6.7	0.8	22.1
	Related	30	33.0	23.5	43.6	10	33.3	17.3	52.8
Diarrhea	Total	16	17.6	10.4	27.0	5	16.7	5.6	34.7
	Grade 2 or 3	12	13.2	7.0	21.9	3	10.0	2.1	26.5
	Grade 3	8	8.8	3.9	16.6	0	0.0	0.0	11.6
	Related	11	12.1	6.2	20.6	3	10.0	2.1	26.5
Irritability/ fussiness	Total	49	53.8	43.1	64.4	20	66.7	47.2	82.7
	Grade 2 or 3	24	26.4	17.7	36.7	11	36.7	19.9	56.1
	Grade 3	6	6.6	2.5	13.8	1	3.3	0.1	17.2
	Related	42	46.2	35.6	56.9	18	60.0	40.6	77.3
Loss of appetite	Total	37	40.7	30.5	51.5	12	40.0	22.7	59.4
	Grade 2 or 3	18	19.8	12.2	29.4	5	16.7	5.6	34.7
	Grade 3	4	4.4	1.2	10.9	1	3.3	0.1	17.2
	Related	31	34.1	24.5	44.7	8	26.7	12.3	45.9
Fever	Total	46	50.5	39.9	61.2	17	56.7	37.4	74.5
	Grade 2 or 3	20	22.0	14.0	31.9	5	16.7	5.6	34.7
	Grade 3	2	2.2	0.3	7.7	1	3.3	0.1	17.2
	Related	41	45.1	34.6	55.8	15	50.0	31.3	68.7
Vomiting	Total	25	27.5	18.6	37.8	7	23.3	9.9	42.3
	Grade 2 or 3	12	13.2	7.0	21.9	5	16.7	5.6	34.7
	Grade 3	3	3.3	0.7	9.3	2	6.7	0.8	22.1
	Related	22	24.2	15.8	34.3	6	20.0	7.7	38.6

Notes: N = number of subjects having received Dose 3 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 3 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

8.5.2.3 Unsolicited symptoms

Supplement 174 presents the percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms from Day 0 to Day 42 after any vaccination.

The percentage of subjects reporting at least one unsolicited symptoms from Day 0 to Day 42 after vaccination were similar between the groups: 90.3% in the HRV $10^{4.7}$ group, 96.7% in the HRV $10^{5.2}$ group, 100% in the HRV $10^{5.8}$ group and 100% in the placebo group.

Table 48 presents the percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from Day 0 to Day 42 after any vaccination. Only one unsolicited symptom reported by a subject in the placebo group was assessed as related to vaccination.

Table 48: The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV $10^{4.7}$ N = 31				HRV $10^{5.2}$ N = 30				HRV $10^{5.8}$ N = 30			
				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		0	0	0	11.2	0	0	0	11.6	0	0	0	11.6
Respiratory system (1100)	Pneumonia (0528)	0	0	0	11.2	0	0	0	11.6	0	0	0	11.6

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 48 (continued): The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)

WHO Body System (CODE)	WHO Preferred term (CODE)	Pooled HRV groups N = 91				Placebo N = 30			
				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL
At least one symptom		0	0	0	4	1	3.3	0.1	17.2
Respiratory system (1100)	Pneumonia (0528)	0	0	0	4	1	3.3	0.1	17.2

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 49 presents the percentage of subjects with grade 3 unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination. The percentage of subjects with grade "3" unsolicited symptoms from Day 0 to Day 42 after vaccination were similar between the groups.

Table 49: The percentage of subjects with grade 3 unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV $10^{4.7}$ N = 31				HRV $10^{5.2}$ N = 30				HRV $10^{5.8}$ N = 30			
				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		1	3.2	0.1	16.7	4	13.3	3.8	30.7	2	6.7	0.8	22.1
Gastrointestinal system (600)	Gastroenteritis (0293)	1	3.2	0.1	16.7	0	0	0	11.6	2	6.7	0.8	22.1
Respiratory system (1100)	Pneumonia (0528)	0	0	0	11.2	4	13.3	3.8	30.7	0	0	0	11.6

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 49 (continued): The percentage of subjects with grade 3 unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)

WHO Body System (CODE)	WHO Preferred term (CODE)	Pooled HRV groups N = 91				Placebo N = 30			
				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL
At least one symptom		7	7.7	3.1	15.2	4	13.3	3.8	30.7
Gastrointestinal system (600)	Gastroenteritis (0293)	3	3.3	0.7	9.3	3	10	2.1	26.5
Respiratory system (1100)	Pneumonia (0528)	4	4.4	1.2	10.9	1	3.3	0.1	17.2

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 175, Supplement 176 and Supplement 177 respectively present percentage of doses with any, related and grade 3 unsolicited symptoms from Day 0 to Day 42 after any vaccination.

8.5.2.4 Concomitant medications

Table 50 presents the percentage of doses with at least one concomitant medication administered from Day 0 to Day 14 after each study vaccination, by type. Supplement 178 presents the same data for overall doses and by subjects.

Concomitant medications were administered to 25 subjects (80.6%) in the HRV $10^{4.7}$ group, 24 subjects (80%) in the HRV $10^{5.2}$ group, 29 subjects (96.7%) in the HRV $10^{5.8}$ group and 24 subjects (80%) in the placebo group from Day 0 to Day 14 after vaccination. The majority of subjects in each group received antipyretics from Day 0 to Day 14 after vaccination. The percentages of subjects who took antipyretics from Day 0 to Day 14 were similar between the groups. Administration of a third dose of HRV vaccine or placebo did not result in increase in the percentage of subjects who took medications.

Table 50: Percentage of doses with at least one concomitant medication administered from Day 0 to Day 14 after vaccination, by type (total vaccinated cohort for safety analysis)

	Dose 1											
	HRV $10^{4.7}$ (N=31)				**HRV $10^{5.2}$ (N=30)**				**HRV $10^{45.8}$ (N=30)**			
Type	**n**	**%**	**95% CI LL**	**95% CI UL**	**n**	**%**	**95% CI LL**	**95% CI UL**	**n**	**%**	**95% CI LL**	**95% CI UL**
Any medication	17	54.8	36.0	72.7	19	63.3	43.9	80.1	22	73.3	54.1	87.7
Any antipyretic	17	54.8	36.0	72.7	18	60.0	40.6	77.3	22	73.3	54.1	87.7
Prophylactic antipyretic	0	0.0	0.0	11.2	0	0.0	0.0	11.6	0	0.0	0.0	11.6
Any antibiotic	1	3.2	0.1	16.7	1	3.3	0.1	17.2	0	0.0	0.0	11.6

	Pooled HRV groups (N=91)				**Placebo (N=30)**			
Type	**n**	**%**	**95% CI LL**	**95% CI UL**	**n**	**%**	**95% CI LL**	**95% CI UL**
Any medication	58	63.7	53.0	73.6	17	56.7	37.4	74.5
Any antipyretic	57	62.6	51.9	72.6	17	56.7	37.4	74.5
Prophylactic antipyretic	0	0.0	0.0	4.0	0	0.0	0.0	11.6
Any antibiotic	2	2.2	0.3	7.7	0	0.0	0.0	11.6

	Dose 2											
	HRV $10^{4.7}$ (N=31)				**HRV $10^{5.2}$ (N=30)**				**HRV $10^{45.8}$ (N=30)**			
Type	**n**	**%**	**95% CI LL**	**95% CI UL**	**n**	**%**	**95% CI LL**	**95% CI UL**	**n**	**%**	**95% CI LL**	**95% CI UL**
Any medication	19	61.3	42.2	78.2	13	43.3	25.5	62.6	19	63.3	43.9	80.1
Any antipyretic	19	61.3	42.2	78.2	13	43.3	25.5	62.6	17	56.7	37.4	74.5
Prophylactic antipyretic	0	0.0	0.0	11.2	0	0.0	0.0	11.6	0	0.0	0.0	11.6
Any antibiotic	1	3.2	0.1	16.7	3	10.0	2.1	26.5	1	3.3	0.1	17.2

	Pooled HRV groups (N=91)				**Placebo (N=30)**			
Type	**n**	**%**	**95% CI LL**	**95% CI UL**	**n**	**%**	**95% CI LL**	**95% CI UL**
Any medication	51	56.0	45.2	66.4	15	50.0	31.3	68.7
Any antipyretic	49	53.8	43.1	64.4	14	46.7	28.3	65.7
Prophylactic antipyretic	0	0.0	0.0	4.0	1	3.3	0.1	17.2
Any antibiotic	5	5.5	1.8	12.4	2	6.7	0.8	22.1

Table 50 (continued): Percentage of doses with at least one concomitant medication administered from Day 0 to Day 14 after vaccination, by type (total vaccinated cohort for safety analysis)

	Dose 3											
	HRV $10^{4.7}$ (N=31)				HRV $10^{5.2}$ (N=30)				HRV $10^{45.8}$ (N=30)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL			LL	UL
Any medication	15	48.4	30.2	66.9	11	36.7	19.9	56.1	16	53.3	34.3	71.7
Any antipyretic	12	38.7	21.8	57.8	10	33.3	17.3	52.8	15	50.0	31.3	68.7
Prophylactic antipyretic	0	0.0	0.0	11.2	0	0.0	0.0	11.6	0	0.0	0.0	11.6
Any antibiotic	4	12.9	3.6	29.8	0	0.0	0.0	11.6	2	6.7	0.8	22.1

	Pooled HRV groups (N=91)				Placebo (N=30)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL
Any medication	42	46.2	35.6	56.9	14	46.7	28.3	65.7
Any antipyretic	37	40.7	30.5	51.5	14	46.7	28.3	65.7
Prophylactic antipyretic	0	0.0	0.0	4.0	0	0.0	0.0	11.6
Any antibiotic	6	6.6	2.5	13.8	1	3.3	0.1	17.2

Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For each dose:
N = number of subjects having received the considered dose of HRV vaccine or placebo
n/% = number/percentage of subjects who started taking the specified concomitant medication at least once from Day 0 to Day 14 after vaccination

8.5.3 Serious adverse events

Appendix: Serious Adverse Events presents a summary table for the SAEs reported until the end of the first efficacy follow-up period.

Among the subjects who received three doses of HRV vaccine or placebo, 27 subjects (6 in the HRV $10^{4.7}$ group, 6 in the HRV $10^{5.2}$ group, 8 in the HRV $10^{5.8}$ group and 7 in the placebo group) reported at least one SAE until the end of the first efficacy follow-up period. All subjects reporting SAEs recovered.

One SAE was assessed as possibly related to vaccination by the respective investigator. Description of the possibly related SAE is given below:

- [redacted]

There were no fatalities or IS in the subset receiving three doses of HRV vaccine or placebo.

8.6 Analysis of immunogenicity

8.6.1 Data sets analyzed

Analysis of immunogenicity was performed only on the total immunogenicity cohort. See Section 3.15.4 for definition of cohorts identified for analyses.

8.6.2 Total vaccinated cohort for immunogenicity analysis

The total vaccinated cohort for analysis of efficacy consisted of 121 subjects (31 subjects in the $10^{4.7}$ ffu HRV vaccine group, 30 subjects in the $10^{5.2}$ ffu HRV vaccine group, 30 subjects in the $10^{5.8}$ ffu HRV vaccine group and 30 subjects the placebo group).

8.6.2.1 Immunogenicity of GSK Biologicals' HRV vaccine

Anti-rotavirus IgA antibody GMCs and seropositivity rates at each sampling timepoint are presented in Table 51.

Seropositivity rates in the three vaccine groups at two months after Dose 2 of HRV vaccine or placebo and at two months after Dose 3 of HRV vaccine or placebo were similar. A trend toward higher anti-rotavirus IgA antibody GMCs at two months after Dose 2 of HRV vaccine or placebo and at two months after Dose 3 of HRV vaccine or placebo was observed in the $10^{5.8}$ ffu HRV vaccine group as compared to the other vaccine groups.

Table 51: Anti-rotavirus IgA antibody GMCs and seropositivity rates (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	≥20 U/ml				GMC (U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	Pre	31	1	3.2	0.1	16.7	<20.0	-	-
	PII(M4)	31	23	74.2	55.4	88.1	54.7	33.6	89.2
	PIII(M6)	31	27	87.1	70.2	96.4	83.3	51.3	135.0
HRV $10^{5.2}$	Pre	29	2	6.9	0.8	22.8	<20.0	-	-
	PII(M4)	29	18	62.1	42.3	79.3	58.6	31.8	108.0
	PIII(M6)	29	21	72.4	52.8	87.3	93.5	46.3	188.9
HRV $10^{5.8}$	Pre	30	1	3.3	0.1	17.2	<20.0	-	-
	PII(M4)	28	20	71.4	51.3	86.8	78.2	41.3	148.1
	PIII(M6)	30	25	83.3	65.3	94.4	128.7	73.8	224.4
Placebo	Pre	28	2	7.1	0.9	23.5	<20.0	-	-
	PII(M4)	28	4	14.3	4.0	32.7	<20.0	-	-
	PIII(M6)	30	8	26.7	12.3	45.9	27.1	13.5	54.4

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Pre = pre-vaccination
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Supplement 179 and Supplement 180 respectively present reverse cumulative distribution curves of anti-rotavirus IgA antibody concentrations in the HRV vaccine group two months after Dose 2 of HRV vaccine or placebo and two months after Dose 3 of HRV vaccine or placebo.

The anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies are presented in Table 52.

Table 52: Anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	GMC (U/ml)		
			Value	95% CI	
				LL	UL
HRV $10^{4.7}$	Pre	1	30.0	-	-
	PII(M4)	23	98.8	64.1	152.4
	PIII(M6)	27	114.0	73.7	176.1
HRV $10^{5.2}$	Pre	2	162.8	-	-
	PII(M4)	18	172.9	105.5	283.3
	PIII(M6)	21	219.1	114.8	418.5
HRV $10^{5.8}$	Pre	1	396.0	-	-
	PII(M4)	20	177.9	103.0	307.5
	PIII(M6)	25	214.5	140.7	327.1
Placebo	Pre	2	519.3	-	-
	PII(M4)	4	201.8	10.8	3786.8
	PIII(M6)	8	419.9	105.5	1672.2

Notes: N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Pre = pre-vaccination
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Table 53 presents the number of subjects with vaccine virus in stool samples collected at pre-determined timepoints.

None of the stool samples collected on the day of Dose 3 of HRV vaccine or placebo (approximately 2 months after Dose 2 of HRV vaccine or placebo) were RV positive, except for a stool sample from one subject in the placebo group.

The percentages of vaccinees with RV shedding at Day 7 after Dose 3 of HRV vaccine or placebo ranged from 7.1% to 10.7% between the vaccine groups.

Table 53: Number of subjects with vaccine virus in stool samples collected at pre-determined timepoints (total vaccinated cohort for immunogenicity analysis)

Group	Shedding Dose 3 [Day –1, Day 0]			Day 7 [Day 6 to Day 10]		
	N	n	%	N	n	%
HRV $10^{4.7}$	27	0	0.0	28	3	10.7
HRV $10^{5.2}$	25	0	0.0	28	2	7.1
HRV $10^{5.8}$	27	0	0.0	30	3	10.0
Placebo	26	1	3.8	30	1	3.3

Notes: N = number of subject with available stool results at the specified time point
n/% = number/percentage of subjects with rotavirus in stool collected at the specified time point

8.6.2.2 Immunogenicity of routine vaccinations (DTPw-HB+Hib and OPV)

Virtually all subjects received the DTPw-HB+Hib vaccine concomitantly with Dose 1, Dose 2 and Dose 3 of HRV vaccine or placebo. None of the subjects received OPV concomitantly with any dose of HRV vaccine or placebo. (refer to Section 8.2.4)

For immunogenicity analyses of concomitant vaccines, the Study Month 4 (two months after Dose 2 of HRV vaccine or placebo) timepoint explores the impact of two doses of HRV vaccine, as compared to placebo, on the immune responses of two doses of concomitantly administered routine DTPw-HB+Hib vaccine and two doses of OPV vaccine given separately from the study vaccines. The Study Month 6 (two months after Dose 3 of HRV vaccine or placebo) timepoint explores the impact of three doses of HRV vaccine, as compared to placebo, on the immune responses of three doses of concomitantly administered routine DTPw-HB+Hib vaccine and three doses of OPV vaccine given separately from the study vaccines. It should be noted that the immunogenicity data at Study Month 6 represents immunogenicity of the complete three-dose primary vaccination course of routine vaccines.

Two months after Dose 3 of HRV vaccine or placebo, the majority of subjects had seroprotective levels of anti-diphtheria, anti-tetanus, anti-HBs, anti-PRP (≥ 0.15 mcg/ml and ≥ 1 mcg/ml) and anti-poliovirus types 1, 2 and 3 antibodies and were seropositive for anti-BPT antibodies.

Antibody responses to all routine vaccine antigens at two months after Dose 2 of HRV vaccine or placebo and two months after Dose 3 of HRV vaccine or placebo (after completion of the primary vaccination course) in the three HRV vaccine groups were similar to those of the placebo (control) indicating that there that there appears to be no impact of HRV vaccine on immunogenicity of OPV and concomitantly administered DTPw-HB+Hib vaccine.

Antibody responses to each of the routine vaccine antigens at each timepoint are presented hereafter.

Anti-diphtheria antibody response

Anti-diphtheria antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 54. Supplement 181 presents reverse cumulative distribution curves of anti-diphtheria antibody concentrations two months after Dose 3 of HRV vaccine or placebo.

Table 54: Anti-diphtheria antibody GMCs and seroprotection rates (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	≥ 0.1 IU/ml				GMC (IU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	30	17	56.7	37.4	74.5	0.151	0.094	0.241
	PIII(M6)	31	26	83.9	66.3	94.5	0.501	0.291	0.863
HRV $10^{5.2}$	PII(M4)	30	17	56.7	37.4	74.5	0.149	0.090	0.246
	PIII(M6)	30	29	96.7	82.8	99.9	0.866	0.579	1.295
HRV $10^{5.8}$	PII(M4)	30	15	50.0	31.3	68.7	0.115	0.078	0.170
	PIII(M6)	30	29	96.7	82.8	99.9	0.772	0.520	1.145
Pooled HRV groups	PII(M4)	90	49	54.4	43.6	65.0	0.137	0.107	0.177
	PIII(M6)	91	84	92.3	84.8	96.9	0.692	0.535	0.895
Placebo	PII(M4)	27	16	59.3	38.8	77.6	0.185	0.106	0.323
	PIII(M6)	30	25	83.3	65.3	94.4	0.498	0.280	0.884

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Anti-tetanus antibody response

Anti-tetanus antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 55. Supplement 182 presents reverse cumulative distribution curves of anti-tetanus antibody concentrations two months after Dose 3 of HRV vaccine or placebo.

Table 55: Anti-tetanus antibody GMCs and seroprotection rates (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	≥ 0.1 IU/ml				GMC (IU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	31	31	100	88.8	100	1.215	0.878	1.681
	PIII(M6)	31	31	100	88.8	100	4.241	3.271	5.500
HRV $10^{5.2}$	PII(M4)	30	30	100	88.4	100	1.964	1.378	2.799
	PIII(M6)	30	30	100	88.4	100	5.397	4.173	6.980
HRV $10^{5.8}$	PII(M4)	30	30	100	88.4	100	1.725	1.270	2.343
	PIII(M6)	30	30	100	88.4	100	4.468	3.465	5.761
Pooled HRV groups	PII(M4)	91	91	100	96.0	100	1.598	1.325	1.927
	PIII(M6)	91	91	100	96.0	100	4.672	4.044	5.397
Placebo	PII(M4)	29	29	100	88.1	100	1.989	1.547	2.558
	PIII(M6)	30	30	100	88.4	100	3.647	2.871	4.633

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Anti-BPT antibody response

Anti-BPT antibody GMCs and seropositivity rates at each sampling timepoint are presented in Table 56. Supplement 183 presents reverse cumulative distribution curves of anti-BPT antibody concentrations two months after Dose 3 of HRV vaccine or placebo.

Table 56: Anti-BPT antibody GMCs and seropositivity rates (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	≥ 15 EL.U/ml				GMC (EL.U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	31	27	87.1	70.2	96.4	25.2	19.8	32.1
	PIII(M6)	31	31	100	88.8	100	106.8	84.9	134.3
HRV $10^{5.2}$	PII(M4)	30	21	70.0	50.6	85.3	26.0	17.8	37.9
	PIII(M6)	30	30	100	88.4	100	104.6	76.7	142.6
HRV $10^{5.8}$	PII(M4)	30	23	76.7	57.7	90.1	24.9	18.6	33.3
	PIII(M6)	29	29	100	88.1	100	109.2	88.3	135.0
Pooled HRV groups	PII(M4)	91	71	78.0	68.1	86.0	25.4	21.4	30.1
	PIII(M6)	90	90	100	96.0	100	106.8	92.8	123.0
Placebo	PII(M4)	29	21	72.4	52.8	87.3	22.9	16.5	31.8
	PIII(M6)	30	30	100	88.4	100	82.0	60.3	111.5

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered level of seropositivity
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Anti-HBs antibody response

Anti-HBs antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 57. Supplement 184 presents reverse cumulative distribution curves of anti-HBs antibody concentrations two months after Dose 3 of HRV vaccine or placebo.

Table 57: Anti-HBs antibody GMCs and seroprotection rates (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	≥ 10 mIU/ml				GMC (mIU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	31	29	93.5	78.6	99.2	389.386	203.756	744.133
	PIII(M6)	31	30	96.8	83.3	99.9	932.074	514.554	1688.38
HRV $10^{5.2}$	PII(M4)	30	29	96.7	82.8	99.9	736.301	412.463	1314.40
	PIII(M6)	30	30	100	88.4	100	1534.89	854.513	2756.98
HRV $10^{5.8}$	PII(M4)	30	30	100	88.4	100	796.338	478.171	1326.21
	PIII(M6)	30	30	100	88.4	100	1619.64	960.522	2731.05
Pooled HRV groups	PII(M4)	91	88	96.7	90.7	99.3	608.171	436.927	846.531
	PIII(M6)	91	90	98.9	94.0	100	1318.18	957.176	1815.35
Placebo	PII(M4)	29	29	100	88.1	100	650.523	426.515	992.183
	PIII(M6)	30	30	100	88.4	100	1139.23	733.341	1769.78

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Anti-PRP antibody response

Anti-PRP antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 58. Supplement 185 presents reverse cumulative distribution curves of anti-PRP antibody concentrations two months after Dose 3 of HRV vaccine or placebo.

Table 58: Anti-PRP antibody GMCs and seroprotection rates (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	≥ 0.15 mcg/ml				≥ 1 mcg/ml				GMC (mcg/ml)		
					95% CI		n	%	95% CI		Value	95% CI	
			n	%	LL	UL			LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	28	28	100	87.7	100	26	92.9	76.5	99.1	5.795	3.606	9.315
	PIII(M6)	31	31	100	88.8	100	31	100	88.8	100	9.376	6.641	13.236
HRV $10^{5.2}$	PII(M4)	30	30	100	88.4	100	25	83.3	65.3	94.4	4.957	3.297	7.451
	PIII(M6)	30	30	100	88.4	100	30	100	88.4	100	8.598	6.326	11.686
HRV $10^{5.8}$	PII(M4)	30	30	100	88.4	100	30	100.0	88.4	100	7.534	5.569	10.193
	PIII(M6)	30	30	100	88.4	100	30	100	88.4	100	8.874	6.700	11.754
Pooled HRV groups	PII(M4)	88	88	100	95.9	100	81	92.0	84.3	96.7	6.009	4.806	7.513
	PIII(M6)	91	91	100	96.0	100	91	100	96.0	100	8.948	7.521	10.646
Placebo	PII(M4)	29	29	100	88.1	100	28	96.6	82.2	99.9	5.366	3.541	8.134
	PIII(M6)	30	30	100	88.4	100	29	96.7	82.8	99.9	7.456	5.383	10.327

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Anti-poliovirus types 1, 2 and 3 antibody response

Anti-poliovirus types 1, 2 and 3 antibody GMTs and seroprotection rates at each sampling timepoint are presented in Table 59. Reverse cumulative distribution curves of anti-poliovirus types 1, 2 and 3 antibody titers two months after Dose 3 of HRV vaccine or placebo are presented in Supplement 186 to Supplement 188.

Table 59: Anti-poliovirus types 1, 2 and 3 antibody GMTs and seroprotection rates (total vaccinated cohort for immunogenicity analysis)

Antibody	Group	Timing	N	≥ 1:8 dilution				GMT		
						95% CI		Value	95% CI	
				n	%	LL	UL		LL	UL
Anti-polio 1	HRV $10^{4.7}$	PII(M4)	31	31	100	88.8	100	4005.4	2676.1	5994.8
		PIII(M6)	31	31	100	88.8	100	3238.8	2110.1	4971.1
	HRV $10^{5.2}$	PII(M4)	30	28	93.3	77.9	99.2	1888.9	925.5	3855.2
		PIII(M6)	30	30	100	88.4	100	2071.7	1444.8	2970.8
	HRV $10^{5.8}$	PII(M4)	30	29	96.7	82.8	99.9	1701.7	878.8	3295.2
		PIII(M6)	29	29	100	88.1	100	2148.2	1370.5	3367.2
	Pooled HRV groups	PII(M4)	91	88	96.7	90.7	99.3	2357.6	1670.5	3327.3
		PIII(M6)	90	90	100	96.0	100	2444.8	1935.3	3088.4
	Placebo	PII(M4)	29	28	96.6	82.2	99.9	1379.2	643.1	2957.6
		PIII(M6)	30	30	100	88.4	100	1335.6	784.9	2272.8
Anti-polio 2	HRV $10^{4.7}$	PII(M4)	31	31	100	88.8	100	2239.5	1506.4	3329.6
		PIII(M6)	31	31	100	88.8	100	1619.7	1066.2	2460.4
	HRV $10^{5.2}$	PII(M4)	30	28	93.3	77.9	99.2	831.6	414.1	1669.7
		PIII(M6)	30	30	100	88.4	100	1035.7	643.8	1665.9
	HRV $10^{5.8}$	PII(M4)	30	29	96.7	82.8	99.9	891.6	518.4	1533.2
		PIII(M6)	29	29	100	88.1	100	976.1	655.5	1453.6
	Pooled HRV groups	PII(M4)	91	88	96.7	90.7	99.3	1192.5	863.6	1646.5
		PIII(M6)	90	90	100	96.0	100	1185.3	928.2	1513.7
	Placebo	PII(M4)	29	28	96.6	82.2	99.9	1153.9	629.2	2116.2
		PIII(M6)	30	30	100	88.4	100	1415.0	886.9	2257.6
Anti-polio 3	HRV $10^{4.7}$	PII(M4)	31	23	74.2	55.4	88.1	84.7	39.6	181.2
		PIII(M6)	31	28	90.3	74.2	98.0	185.0	99.1	345.2
	HRV $10^{5.2}$	PII(M4)	30	19	63.3	43.9	80.1	55.0	23.2	130.4
		PIII(M6)	30	24	80.0	61.4	92.3	125.2	58.4	268.3
	HRV $10^{5.8}$	PII(M4)	30	16	53.3	34.3	71.7	45.3	18.3	112.1
		PIII(M6)	29	22	75.9	56.5	89.7	77.3	33.2	180.3
	Pooled HRV groups	PII(M4)	91	58	63.7	53.0	73.6	59.8	37.3	95.7
		PIII(M6)	90	74	82.2	72.7	89.5	122.6	80.6	186.6
	Placebo	PII(M4)	29	18	62.1	42.3	79.3	64.0	25.1	163.6
		PIII(M6)	30	26	86.7	69.3	96.2	174.8	88.3	346.0

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

9 Discussion

This dose exploration study was conducted in Brazil, Mexico and Venezuela to assess the efficacy, reactogenicity, safety and immunogenicity of two doses of GSK Biologicals' live attenuated HRV vaccine belonging to the serotype G1P1A and genotype [P8]. A total of 2155 infants aged 6 to 12 weeks old were enrolled and randomized to receive two doses of one of three different virus concentrations ($10^{4.7}$, $10^{5.2}$ or $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine or placebo concomitantly with routine DTPw-HB+Hib vaccines.

The sample size in this study was large enough to reach a sufficient number of RV GE cases and demonstrate vaccine efficacy against any RV GE (primary endpoint), severe (≥ 11 points on a 20-point scale) RV GE and against hospitalization due to RV GE from two weeks after Dose 2 of HRV vaccine or placebo until end of the first efficacy follow-up period (at approximately one year of age).

A significant health burden exists worldwide due to mortality and morbidity in young children due to severe diarrhea and dehydration associated with RV GE. Prevention by vaccination is considered to be critical for effective control of RV disease. In this study, a statistically significant decrease (p-value < 0.05, two-sided Fisher's exact test) in the percentage of infants with any RV GE and severe RV from two weeks after Dose 2 of HRV vaccine or placebo until end of the first efficacy follow-up period was detected in pooled HRV vaccine groups and each HRV vaccine group as compared to the placebo group. The protective efficacy after two doses of HRV vaccine against RV GE of any severity ranged from 56% to 70%. The protective efficacy was even higher against severe RV GE (66% to 86%). There was a trend towards better efficacy in the $10^{5.8}$ ffu HRV vaccine group. Vaccine efficacy for the pooled HRV vaccine groups was 61.4% [95% CI, 42.3– 74.1] against any RV GE and 74.1% [95% CI, 55.8– 85] against severe RV GE. GSK Biologicals' HRV vaccine thus afforded protection against RV GE illness during the first year of life in susceptible children when severe disease is most common.

During the first efficacy follow-up period, the predominant RV types isolated were wild-type G1 (identified in 50.5% of RV GE episodes) and G9 (identified in 39.4% of RV GE episodes). In addition, G2, G3 and G4 types were also isolated. A statistically significant decrease (p-value < 0.05, two-sided Fisher's exact test) in the percentage of infants with severe RV GE caused by G1 and non-G1 serotypes was detected in pooled HRV vaccine groups as compared to the placebo group. For cases attributed to the wild-type G1 type, vaccine efficacy for the pooled HRV vaccine groups was 71.9% [95% CI, 50.3– 84.2] against any RV GE and 73.5% [95% CI, 41.2– 88.3] against severe RV GE. For cases attributed to the non-G1 types, vaccine efficacy for the pooled HRV vaccine groups was 49.4% [95% CI, 6.4– 72.1] against any RV GE and 73.1% [95% CI, 42.7– 87.7] against severe RV GE. Proof of concept that GSK Biologicals' monovalent G1[P8] HRV vaccine exhibits clinical protection against homologous and heterotypic strains was thus demonstrated in the Latin American setting where G1 and non-G1 serotypes were circulating.

In each country, a statistically significant decrease (p-value < 0.05, two-sided Fisher's exact test) in the percentage of infants with any and severe RV GE was detected in pooled HRV vaccine groups as compared to the placebo.

Efficacy of the HRV vaccine against any and severe RV GE was apparent from the day of Dose 1 onwards and this is an important parameter for public health considerations since efficacy was evident immediately after administration of the first dose.

A statistically significant decrease (p-value < 0.05, two-sided Fisher's exact test) in the percentage of infants hospitalized due to RV GE was detected in pooled HRV vaccine groups as compared to the placebo group. Vaccine efficacy for the pooled HRV vaccine groups was 79.0% [95% CI, 48.0– 92.0] against hospitalization due to RV GE. The vaccine efficacy against hospitalization was confirmed for the highest viral concentration. The data on vaccine efficacy against hospitalization for each viral concentration should be interpreted cautiously due to the limited number of hospitalization reported (9 in the pooled HRV vaccine groups and 14 in the placebo group).

Vaccine efficacy rates observed in this study (pooled HRV vaccine groups) against any and severe RV GE caused by homotypic G1 strains were similar to vaccine efficacy rates observed during a pilot efficacy trial with GSK Biologicals' HRV vaccine ($10^{4.7}$ ffu) in Finland ([10]) and efficacy of the parent 89-12 strain (10^5 ffu) in USA ([2]). The tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV) that was licensed in the USA in 1998 but then withdrawn in 1999 because of association with intussusception ([11], [12]) showed better efficacy in developed countries than in developing countries ([13], [14], [15], [16]). Efficacy of two doses of GSK Biologicals'

HRV vaccine (pooled HRV vaccine groups) compared favorably with the efficacy of three doses of RRV-TV (4 x 10^5 plaque forming units) in Venezuela ([15]). RRV-TV (4 x 10^4 plaque forming units) had only limited efficacy in Brazil ([17]). On the other hand, GSK Biologicals' HRV vaccine (pooled HRV vaccine groups) was efficacious against any and severe RV GE in all three countries (Brazil, Mexico and Venezuela).

Solicited and unsolicited symptoms were reported at similar frequencies in the HRV vaccine and placebo groups during the 15-day solicited follow-up period after each dose and there was no increase in reactogenicity from Dose 1 to Dose 2 or with increasing viral concentrations. In contrast, mild febrile reactions have been reported at a higher rate following administration of parent 89-12 strain ([2]) and RRV-TV ([5]) compared to placebo. When looking at the reactogenicity data by country, the incidence rates were similar between the HRV vaccine groups and the placebo within each country. The observed differences in reactogenicity between countries can be attributed to country-specific customs and practices.

GSK Biologicals' HRV vaccine elicited an immune response in terms of seroconversion for anti-rotavirus IgA antibodies in 60.6–65.3% of subjects two months after two doses of HRV vaccine. Persistence in terms of anti-rotavirus IgA antibody levels at approximately 8 months after Dose 2 of HRV vaccine was similar in the three HRV vaccine groups but IgA antibody levels were higher than at two months after Dose 2. This could most likely be due to natural RV infection. There was no significant increase in anti-rotavirus IgA antibody GMCs from Dose 1 to Dose 2 indicating catch-up effect (response to Dose 2 in subjects who were seronegative after Dose 1) rather than booster effect (significant increase in antibody concentrations after Dose 2 in subjects who were seropositive after Dose 1). RV shedding was seen mainly at Day 7 after the first dose with very little detectable HRV shedding observed 60 days after the first dose. There was a trend towards a better immunogenicity profile (in terms of IgA seroconversion rates, GMCs and vaccine take) in the $10^{5.8}$ ffu HRV vaccine group and immunogenicity observed in this group compared favourably with the parent 89-12 strain ([2]).

Anti-rotavirus IgA antibodies are considered as a strong marker of protection, though no correlate of protection against RV infection and disease has yet been identified ([18], [19]). Even though serological status of anti-rotavirus IgA antibodies two months after Dose 2 was known only for a subset of subjects, subjects in the pooled HRV vaccine groups who had seroconverted at two months post Dose 2 appeared less likely to develop RV GE during the first efficacy follow-up period: 11.2% (95% CI, 6.9–17.0) of seronegative subjects had RV GE *versus* 1.6% (95% CI, 0.5–3.7) of seropositive (seroconverted) subjects.

Immunogenicity of routine vaccines was evaluated two months after the second dose of HRV vaccine or placebo. Two months after the second dose, more than 58% of vaccinees had protective anti-diphtheria antibodies and more than 97% of subjects had protective anti-tetanus and anti-HBs antibodies. More than 99% of subjects had anti-PRP antibody level ≥ 0.15 mcg/ml and more than 88% had anti-PRP antibody level ≥ 1.0 mcg/ml. At least 84% of subjects had protective levels of neutralizing antibodies to each poliovirus serotypes. Seropositivity rate against anti-BPT antibodies were at least 59%. It should be noted that the complete routine vaccination course consists of three doses. Antibody responses (in terms of seroprotection/seropositivity rates and GMC/Ts) to all vaccine antigens contained in concomitantly administered routine DTPw-HB+Hib vaccine at two months after Dose 2 of HRV vaccine or placebo were similar between the three HRV vaccine groups and the placebo (control). Also, persistence at approximately one year of age in all HRV vaccine groups was similar to the placebo. Thus, there appeared to be no impact of HRV vaccine on immunogenicity of concomitantly administered routine vaccines. Also, there was no apparent impact of HRV vaccine on immunogenicity of OPV vaccine given separately from HRV vaccine with a two week interval as seen from similar serprotection rates to the three poliovirus serotypes between the three HRV vaccine groups and the placebo.

Administration of a third dose of GSK Biologicals' HRV vaccine or placebo was an exploratory evaluation. Due to the small number of subjects who received a third dose of HRV vaccine or placebo, the results obtained should be interpreted with caution. An additional dose or the higher age of the subjects in this cohort did not appear to impact on the reactogenicity profile of the HRV vaccine as compared to the placebo. There was a trend towards higher immunogenicity (in terms of anti-rotavirus IgA antibody GMCs) in the $10^{5.8}$ ffu HRV vaccine group two months after Dose 2 and Dose 3 of HRV vaccine. Seroprotection/seropositivity rates and GMC/Ts were high in all groups after completion of the three-dose primary vaccination course of routine DTPw-HB+Hib and OPV vaccines. There appeared to be no impact of HRV vaccine on immunogenicity of OPV and concomitantly administered DTPw-HB+Hib vaccine two months after the third dose of HRV vaccine or placebo.

10 Overall Conclusions

Study rota-006 demonstrated that two doses of GSK Biologicals' HRV vaccine were well tolerated, immunogenic and efficacious in protecting susceptible infants until approximately one year of age against RV GE in the Latin American setting where G1 and non-G1 RV serotypes were circulating. The highest viral concentration ($10^{5.8}$ ffu) evaluated showed higher immunogenicity and protection without increased reactogenicity.

Efficacy

- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups and each viral concentration) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of any RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The observed vaccine efficacy ranged between 55.7% to 70%. Thus, the primary objective of the study was met.

- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups and each viral concentration) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of severe RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The observed vaccine efficacy ranged between 65.8% to 85.6%.

- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of hospitalization due to RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The observed vaccine efficacy in pooled HRV vaccine groups was 79%.

- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of any and severe RV GE caused by G1 and non-G1 serotypes relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. Proof of concept that GSK Biologicals' monovalent G1[P8] HRV vaccine exhibits clinical protection against homotypic and heterotypic strains was thus demonstrated in the Latin American setting where G1 and non-G1 serotypes were circulating.

- The highest viral concentration of GSK Biologicals' HRV vaccine evaluated, $10^{5.8}$ ffu, consistently performed better in terms of homotypic and heterotypic protection against any and severe RV GE.

Safety/Reactogenicity

- The safety and reactogenicity profile of two doses of each viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations was similar to that of the placebo in terms of the incidences of solicited/unsolicited symptoms and SAEs reported after vaccination. There was no increase in reactogenicity with the use of higher viral concentration and from Dose 1 to Dose 2.

- Even the highest viral concentration used, HRV vaccine at $10^{5.8}$ ffu, did not result in increased reactogenicity as compared to placebo, confirming the mild reactogenicity profile of GSK Biologicals' attenuated HRV vaccine.

Immunogenicity

- Vaccine take rates ranged from 48.6% to 57.4% at two months after the first dose of GSK Biologicals' HRV vaccine containing $10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu. Vaccine take rates ranged from 62.6% to 69.1% at two months after the second dose.

- Persistence in terms of serum anti-rotavirus IgA antibodies at the end of the first efficacy follow-up period (approximately 8 months after the second dose) was similar for the three viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine.

- RV shedding was observed predominantly after Dose 1 of GSK Biologicals' HRV vaccine with little residual shedding two months after Dose 1.

- There was a trend towards higher immunogenicity in terms of IgA seroconversion rates, GMCs and vaccine take in the $10^{5.8}$ ffu HRV vaccine group at two months after Dose 2.

- The effect of unrestricted feeding on the immunogenicity of GSK Biologicals' HRV vaccine was evaluated and indicated that none of the pre-defined feeding criteria had a significant effect.

- GSK Biologicals' HRV vaccine did not appear to impact on immunogenicity of routine vaccines, DTPw-HB and Hib (given concomitantly) or OPV vaccine.

Exploratory evaluation of three doses of HRV vaccine in a subset of subjects

- Within the limits of the small sample size, three doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups and each viral concentration) given concomitantly to healthy infants with routine vaccinations appeared to decrease the incidence of any and severe RV GE relative to the placebo during the period starting from 2 weeks after Dose 3 until the end of the first efficacy follow-up period.

- The safety and reactogenicity profile of the three doses of each viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations was similar to that of the placebo in terms of the incidences of solicited/unsolicited symptoms and SAEs reported after vaccination.

- Anti-rotavirus IgA antibody responses in terms of seropositivity and GMCs were similar for the three viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) at two months after the second dose and at two months after the third dose of GSK Biologicals' HRV vaccine. There was a trend towards higher immunogenicity in the $10^{5.8}$ ffu HRV vaccine group.

- RV shedding observed after the third dose of GSK Biologicals' HRV vaccine was similar for the three viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu).

- GSK Biologicals' HRV vaccine did not appear to impact on immunogenicity of routine vaccines, DTPw-HB and Hib (given concomitantly) or OPV vaccine.

11 References

[1] Bernstein DI, Smith VE, Sherwood JR, Schiff GM, Sander DS, DeFeudis D, Spriggs DR, Ward RL. Safety and immunogenicity of a live attenuated human rotavirus 89-12 vaccine. Vaccine 1998;16:381–7.

[2] Bernstein DI, Sack DA, Rothstein E, Reisinger K, Smith VE, O'Sullivan D, Spriggs DR, Ward RL. Efficacy of live attenuated human rotavirus vaccine 89-12 in infants: a randomized placebo-controlled trial. Lancet 1999;354:287–90.

[3] White SJ and Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. Br J Cancer 1978;37:849–57.

[4] Ruuska T and Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for severity of diarrheal episodes. Scand J Infect Dis 1990;22:259–67.

[5] Joensuu J, Koskenniemi E, Pang X-L, Vesikari T. Randomized placebo-controlled trial of dose rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis. Lancet 1997;350:1205–9.

[6] Ward RL, Bernstein DI, Shukla R, *et al*. Effects of antibody to Rotavirus on protection of adults challenged with a human Rotavirus. J. Infect. Dis. 1989; 159:79–88.

[7] Melville-Smith M, Balfour A. Estimation of Corynebacterium diphtheria antitoxin in human sera: a comparison of an enzyme-linked immunosorbent assay with the toxin Neutralisation test. J Med Microbiol 1988; 24:279–83.

[8] Melville-Smith ME, Seagroatt VA, Watkins JT. A comparison of enzyme linked immunosorbent assay (ELISA) with the toxin Neutralisation test in mice as a method for the estimation of tetanus antitoxin in human sera. J Biol Stand 1983; 11:137–44.

[9] GSK Biologicals study rota-006, data on file.

[10] Efficacy evaluation of an oral human rotavirus (HRV) vaccine in previously uninfected Finnish infants. Poster presented at Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Diego, USA, Sep 27-30, 2002.

[11] American Academy of Pediatrics. Possible association of intussusception with rotavirus vaccination. Pediatrics 1999;104:575.

[12] CDC. Withdrawal of rotavirus vaccine recommendation. MMWR 1999;48:1007.

[13] Rennels MB, Glass RI, Dennehy PH, Bernstein DI, Pichichero ME, Zito ET. Safety and efficacy of high dose rhesus-human reassortant rotavirus vaccines – report of the National Multicenter Trial. Pediatrics 1996;97:7–13.

[14] Joensuu J, Koskenniemi E, Pang X-L, Vesikari T. Randomised placebo-controlled trial of rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis. Lancet 1997;350:1205 – 9.

[15] Perez-Schael I, Guntinas MJ, Perez M, Pagone V, Rojas A, Gonzales R, Cunto W, Hoshino Y, Kapikan AZ. Efficacy of the rhesus rotavirus-based quadrivalent vaccine in infants and young children in Venezuela. N Engl J Med. 1997;337:1181–7.

[16] Santosham M, Moulton LH, Reid R, Croll J, Weatherholt R, Ward R, Forro J, Zito E, Mack M, Brenneman G, Davidson BL. Efficacy and safety of high dose rhesus-human reassortant rotavirus vaccine in Native American population. J Pediatr 1997;131:632–8.

[17] Linhares Ac, Gabbay YB, Mascarenhas JDP *et al*. Immunogenicity, safety and efficacy of tetravalent rhesus-human, reassortant rotavirus vaccine in Belem, Brazil. Bull World Health Organ 1996;74:491–500.

[18] Ward RL. Mechanisms of protection against rotavirus in humans and mice. J Infect Dis 1996; 174 (Suppl 1);S51–8.

[19] Velaquez FR, Matson DO, Guerrero ML *et al*. Serum antibody as a marker of protection against natural rotavirus infection and disease. J Infect Dis 2000;182.

CONTENTS: SUPPLEMENTS

Supplement 1: Compliance (total vaccinated cohort for subset planned to receive two doses of study vaccine) 187
Supplement 2: Deviations from specifications for age and intervals between study visits (total vaccinated cohort for subset planned to receive two doses of study vaccine) 188
Supplement 3: Percentage of GE episodes with no available stools results from 2 weeks after Dose 2 up to the end of the first efficacy follow-up period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)..189
Supplement 4: Summary of demographic characteristics (age calculated in weeks) (total vaccinated cohort for subset planned to receive two doses of study vaccine) 190
Supplement 5: Summary of demographic characteristics (age calculated in weeks) in Brazil (total vaccinated cohort for subset planned to receive two doses of study vaccine) 191
Supplement 6: Summary of demographic characteristics (age calculated in weeks) in Mexico (total vaccinated cohort for subset planned to receive two doses of study vaccine) 192
Supplement 7: Summary of demographic characteristics (age calculated in weeks) in Venezuela (total vaccinated cohort for subset planned to receive two doses of study vaccine).....193
Supplement 8: Increase in height and weight from Visit 1 to Visit 2, 3 and 4 (total vaccinated cohort for subset planned to receive two doses of study vaccine) ...194
Supplement 9: Summary of demographic characteristics (age calculated in weeks) (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine).....195
Supplement 10: Percentage of subjects who received OPV at birth (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 196
Supplement 11: Summary of feeding criteria (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 196
Supplement 12: Duration (in years) of the follow-up period from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 197
Supplement 13: Percentage of subjects who reported GE episode(s) from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 198
Supplement 14: Characteristics of GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine).....199
Supplement 15: Characteristics of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 200
Supplement 16: Characteristics of RV GE episodes of G1 wild type, reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine).....201
Supplement 17: Characteristics of RV GE episodes of G9 type, reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 202

Supplement 18: Percentage of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period, by mixed infection (ATP cohort for efficacy for subset planned to receive two doses of study vaccine).....203
Supplement 19: Percentage of vaccinees reporting RV GE episodes from 2 weeks after Dose 2 up to the end of the first efficacy period, by status of anti-rotavirus IgA antibody concentration at two months after Dose 2 (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 203
Supplement 20: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (ATP cohort for efficacy for subset planned to receive two doses of study vaccine).....204
Supplement 21: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 205
Supplement 22: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (ATP cohort for efficacy for subset planned to receive two doses of study vaccine).....206
Supplement 23: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 207
Supplement 24: Duration (in years) of the follow-up period from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 208
Supplement 25: Percentage of subjects who reported GE episode(s) from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....209
Supplement 26: Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period, by severity (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 209
Supplement 27: Percentage of subjects with RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....210
Supplement 28: Characteristics of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 211
Supplement 29: Characteristics of RV GE episodes of G1 wild type, reported from 2 weeks after Dose 2 stools up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 212
Supplement 30: Characteristics of RV GE episodes of G9 type, reported from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....213
Supplement 31: Percentage of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period, by mixed infection (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....214

Supplement 32: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....215
Supplement 33: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 216
Supplement 34: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 217
Supplement 35: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....218
Supplement 36: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....219
Supplement 37: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....220
Supplement 38: Percentage of subjects hospitalized due to RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 221
Supplement 39: Percentage of vaccinees reporting RV GE episodes from 2 weeks after Dose 2 up to the end of the first efficacy period, by status of anti-rotavirus IgA antibody concentration at two months after Dose 2 (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....222
Supplement 40: Percentage of subjects who reported any or severe RV GE episode(s) from day of Dose 1 till Day 14 after Dose 2 (total vaccinated cohort for subset planned to receive two doses of study vaccine).....223
Supplement 41: Percentage of subjects who reported any or severe RV GE episode(s) other than vaccine strain and efficacy of the vaccine from day of Dose 1 till Day 14 after Dose 2 (total vaccinated cohort for subset planned to receive two doses of study vaccine) 224
Supplement 42: Percentage of subjects who reported any or severe RV GE episode(s) and efficacy of the vaccine from day of Dose 1 till the end of the first efficacy follow-up period (total vaccinated cohort for subset planned to receive two doses of study vaccine) 225
Supplement 43: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....226
Supplement 44: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15- day follow-up

period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 227
Supplement 45: Percentage of doses and subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 228
Supplement 46: Prevalence of diarrhea by day after vaccination, during the solicited 15-day follow-up period after Dose 1 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 232
Supplement 47: Prevalence of diarrhea by day after vaccination, during the solicited 15-day follow-up period after Dose 2 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 233
Supplement 48: Prevalence of fever by day after vaccination, during the solicited 15-day follow-up period after Dose 1 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 234
Supplement 49: Prevalence of fever by day after vaccination, during the solicited 15-day follow-up period after Dose 2 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 235
Supplement 50: Prevalence of vomiting by day after vaccination, during the solicited 15-day follow-up period after Dose 1 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 236
Supplement 51: Prevalence of vomiting by day after vaccination, during the solicited 15-day follow-up period after Dose 2 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 237
Supplement 52: Duration (in days) of diarrhea, vomiting and fever during the solicited 15-day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 238
Supplement 53: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 239
Supplement 54: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 243
Supplement 55: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 247
Supplement 56: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade “3” from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 248
Supplement 57: Percentage of subjects with gastrointestinal symptoms (unsolicited symptoms), from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 250
Supplement 58: Percentage of doses with gastrointestinal symptoms (unsolicited symptoms), from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 251

Supplement 59: Number and percentage of doses and of subjects who took at least one concomitant medication from Day 0 to Day 14 after vaccination by type (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....252
Supplement 60: Percentage of subjects who took antipyretics after Dose 1, by day from Day 0 to Day 42 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....253
Supplement 61: Percentage of subjects who took antipyretics after Dose 2, by day from Day 0 to Day 42 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....254
Supplement 62: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....255
Supplement 63: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....256
Supplement 64: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....257
Supplement 65: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....258
Supplement 66: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....259
Supplement 67: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....260
Supplement 68: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....261
Supplement 69: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....262
Supplement 70: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....263
Supplement 71: Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded “3” in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....264

Supplement 72: Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded “3” in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 272
Supplement 73: Percentage of doses and of subjects reporting each solicited general symptoms included those graded “3” in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)....280
Supplement 74: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 288
Supplement 75: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 292
Supplement 76: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 295
Supplement 77: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 297
Supplement 78: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 301
Supplement 79: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 303
Supplement 80: Percentage of subjects with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine y)....305
Supplement 81: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)....306
Supplement 82: Percentage of subjects with unsolicited symptoms classified by WHO preferred term with grade “3” from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 307
Supplement 83: Percentage of subjects with unsolicited symptoms classified by WHO preferred term with grade “3” from Day 0 to Day 42 after any vaccination in

Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 308
Supplement 84: Percentage of subjects with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 309
Supplement 85: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 310
Supplement 86: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 311
Supplement 87: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 312
Supplement 88: Number and percentage of subjects who received vaccine dose(s) (ATP cohort for safety for subset planned to receive two doses of study vaccine) 313
Supplement 89: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period (ATP cohort for safety for subset planned to receive two doses of study vaccine) 314
Supplement 90: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period (ATP cohort for safety for subset planned to receive two doses of study vaccine).....315
Supplement 91: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period (ATP cohort for safety for subset planned to receive two doses of study vaccine) 316
Supplement 92: Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine) 317
Supplement 93: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine).....325
Supplement 94: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine).....329
Supplement 95: Percentage of subjects with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine).....333
Supplement 96: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination from Day 0 to Day 42 after any

vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine).....334
Supplement 97: Percentage of subjects with grade "3" unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine) 335
Supplement 98: Percentage of doses with grade "3" unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine) 337
Supplement 99: Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations two months after Dose 2 (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 339
Supplement 100: Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 340
Supplement 101: Results of the exploratory logistic regression to assess impact of feeding criteria on the vaccine take (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 341
Supplement 102: Anti-rotavirus IgA antibody GMC and seroconversion rates in Brazil (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 341
Supplement 103: Anti-rotavirus IgA antibody GMC and seroconversion rates in Mexico (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 342
Supplement 104: Anti-rotavirus IgA antibody GMC and seroconversion rates in Venezuela (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 343
Supplement 105: Anti-rotavirus IgA antibody GMC and seroconversion rates (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine).....344
Supplement 106: Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 345
Supplement 107: Anti-rotavirus IgA antibody GMC and seroconversion rates in Brazil (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 346
Supplement 108: Anti-rotavirus IgA antibody GMC and seroconversion rates in Mexico (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine).....347
Supplement 109: Anti-rotavirus IgA antibody GMC and seroconversion rates in Venezuela (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine).....348
Supplement 110: Anti-rotavirus IgA antibody GMC and seroconversion rates for the stool subset (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine).....349
Supplement 111: Percentage of subjects with rotavirus in stool samples collected at pre-determined time points (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 350

Supplement 112: Percentage of subjects with rotavirus in stool samples collected at pre-determined time points, on combined time points (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 351
Supplement 113: Difference between pooled/each HRV vaccine groups and the placebo group in anti-diphtheria antibody seroprotection rates, at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 351
Supplement 114: Difference between pooled/each HRV vaccine groups and the placebo group in anti-diphtheria antibody seroprotection rates, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 351
Supplement 115: Ratio of anti-diphtheria antibody GMCs between pooled/each HRV vaccine groups and the placebo group, at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 352
Supplement 116: Ratio of anti-diphtheria antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 352
Supplement 117: Reverse cumulative curve for anti-diphtheria antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 353
Supplement 118: Reverse cumulative curve for anti-diphtheria antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 354
Supplement 119: Difference between pooled/each HRV vaccine groups and the placebo group in anti-tetanus antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 355
Supplement 120: Difference between pooled/each HRV vaccine groups and the placebo group in anti-tetanus antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 355
Supplement 121: Ratio of anti-tetanus antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 356
Supplement 122: Ratio of anti-tetanus antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 356
Supplement 123: Reverse cumulative curve for anti-tetanus antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 357
Supplement 124: Reverse cumulative curve for anti-tetanus antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 358

Supplement 125: Difference between pooled/each HRV vaccine groups and the placebo group in anti-BPT antibody seropositivity rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 359
Supplement 126: Difference between pooled/each HRV vaccine groups and the placebo group in anti-BPT seropositivity rates at the end of the first efficacy period (ATP cohort for immunogenicity) 359
Supplement 127: Ratio of anti-BPT antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 360
Supplement 128: Ratio of anti-BPT antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 360
Supplement 129: Reverse cumulative curve for anti-BPT antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 361
Supplement 130: Reverse cumulative curve for anti-BPT antibody concentrations at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 362
Supplement 131: Difference between pooled/each HRV vaccine groups and the placebo group in anti-HBs antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 363
Supplement 132: Difference between pooled/each HRV vaccine groups and the placebo group in anti-HBs antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 363
Supplement 133: Ratio of anti-HBs antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 364
Supplement 134: Ratio of anti-HBs antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 364
Supplement 135: Reverse cumulative curve for anti-HBs antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 365
Supplement 136: Reverse cumulative curve for anti-HBs antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 366
Supplement 137: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP concentrations ≥ 0.15 mcg/ml at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity) 367
Supplement 138: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP antibody concentrations ≥

1 mcg/ml at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)367
Supplement 139: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP antibody concentrations ≥ 0.15 mcg/ml at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 368
Supplement 140: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP antibody concentrations ≥ 1 mcg/ml ml at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 368
Supplement 141: Ratio of anti-PRP antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 369
Supplement 142: Ratio of anti-PRP antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 369
Supplement 143: Reverse cumulative curve for anti-PRP antibody concentrations, at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 370
Supplement 144: Reverse cumulative curve for anti-PRP antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 371
Supplement 145: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 1 antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 372
Supplement 146: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 2 antibody seroprotection at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 372
Supplement 147: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 3 antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 372
Supplement 148: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 1 antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 373
Supplement 149: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 2 antibody seroprotection at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 373
Supplement 150: Difference between pooled/ each HRV vaccine groups and the placebo group in anti-poliovirus type 3 antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 373

Supplement 151: Ratio of anti-poliovirus type 1 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 374
Supplement 152: Ratio of anti-poliovirus type 2 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 374
Supplement 153: Ratio of anti-poliovirus type 3 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 374
Supplement 154: Ratio of anti-poliovirus type 1 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 375
Supplement 155: Ratio of anti-poliovirus type 2 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 375
Supplement 156: Ratio of anti-poliovirus type 3 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 375
Supplement 157: Reverse cumulative curve for anti-poliovirus type 1 antibody titers at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 376
Supplement 158: Reverse cumulative curve for anti-poliovirus type 1 antibody titers at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 377
Supplement 159: Reverse cumulative curve for anti-poliovirus type 2 antibody titers at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 378
Supplement 160: Reverse cumulative curve for anti-poliovirus type 2 antibody titers at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 379
Supplement 161: Reverse cumulative curve for anti-poliovirus type 3 antibody titers at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 380
Supplement 162: Reverse cumulative curve for anti-poliovirus type 3 antibody titers at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 381
Supplement 163: Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 382
Supplement 164: Seropositivity rates and anti-BPT antibody GMCs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 383

Supplement 165: Seroprotection rates and anti-HBs antibody GMCs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 384
Supplement 166: Seroprotection rates and anti-PRP antibody GMCs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 385
Supplement 167: Seroprotection rates and anti-poliovirus types 1, 2 and 3 GMTs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 386
Supplement 168: Summary of demographic characteristics (age calculated in weeks) (total vaccinated cohort receiving three doses of study vaccine)....387
Supplement 169: Increase in height and weight from Visit 1 to Visit 2, 3, 4 and 5 (total vaccinated cohort receiving three doses of study vaccine)....388
Supplement 170: Summary of feeding criteria (total vaccinated cohort receiving three doses of study vaccine) 389
Supplement 171: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine) 390
Supplement 172: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up (total vaccinated cohort for safety receiving three doses of study vaccine) 391
Supplement 173: Percentage of doses and of subjects reporting each solicited general symptoms included those graded “3” and grade “2” or “3” in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine) 392
Supplement 174: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine) 396
Supplement 175: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine) 399
Supplement 176: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine) 402
Supplement 177: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade “3” from day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine) 403
Supplement 178: Number and percentage of doses and subjects who took at least one concomitant medication from Day 0 to Day 14 after vaccination by type (total vaccinated cohort for safety receiving three doses of study vaccine) 404
Supplement 179: Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations two months after Dose 2 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)....405
Supplement 180: Reverse cumulative curves for anti-rotavirus IgA antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine) 406

Supplement 181: Reverse cumulative curves for anti-diphtheria antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine) 407
Supplement 182: Reverse cumulative curves for anti-tetanus antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....408
Supplement 183: Reverse cumulative curves for anti-BPT antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....409
Supplement 184: Reverse cumulative curves for anti-HBs antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....410
Supplement 185: Reverse cumulative curves for anti-PRP antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....411
Supplement 186: Reverse cumulative curves for anti-poliovirus type 1 antibody titers two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....412
Supplement 187: Reverse cumulative curves for anti-poliovirus type 2 antibody titers two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....413
Supplement 188: Reverse cumulative curves for anti-poliovirus type 3 antibody titers two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....414

Supplement 1: Compliance (total vaccinated cohort for subset planned to receive two doses of study vaccine)

Dose	Group	Number of Doses	Doses NOT according to protocol	Number of general SS	Compliance % general
1	HRV_4.7	538	8	528	98.1
	HRV_5.2	540	10	528	97.8
	HRV_5.8	540	10	529	98.0
	Pooled HRV groups	1618	28	1585	98.0
	Placebo	537	16	532	99.1
2	HRV_4.7	510	13	506	99.2
	HRV_5.2	509	19	508	99.8
	HRV_5.8	515	10	512	99.4
	Pooled HRV groups	1534	42	1526	99.5
	Placebo	522	14	517	99.0
Total	HRV_4.7	1048	21	1034	98.7
	HRV_5.2	1049	29	1036	98.8
	HRV_5.8	1055	20	1041	98.7
	Pooled HRV groups	3152	70	3111	98.7
	Placebo	1059	30	1049	99.1

Notes: SS = Symptom sheet
Doses not according to protocol = number of doses with regurgitation

Supplement 2: Deviations from specifications for age and intervals between study visits (total vaccinated cohort for subset planned to receive two doses of study vaccine)

Group	Age	VAC_1-VAC_2	VIS_2-BL_3	VIS_3-BL_4
	Protocol	Protocol	Protocol	Protocol
	from 6 to 12 W	from 49 to 83 D	from 49 to 83 D	from 160 to 200 D
HRV_4.7	/	n = 21 subjects (from -1 to 34 D) 4.1% of 510 (28 subjects with empty value)	n = 23 subjects (from -18 to 28 D) 12.2% of 188 (350 subjects with empty value)	n = 7 subjects (from -26 to 139 D) 1.4% of 492 (46 subjects with empty value)
HRV_5.2	/	n = 32 subjects (from -3 to 36 D) 6.3% of 509 (31 subjects with empty value)	n = 15 subjects (from -17 to 36 D) 8.3% of 181 (359 subjects with empty value)	n = 13 subjects (from -11 to 40 D) 2.6% of 493 (47 subjects with empty value)
HRV_5.8	/	n = 35 subjects (from -1 to 37 D) 6.8% of 515 (25 subjects with empty value)	n = 20 subjects (from -7 to 23 D) 10.8% of 185 (355 subjects with empty value)	n = 10 subjects (from -63 to 37 D) 2.0% of 491 (49 subjects with empty value)
Placebo	/	n = 37 subjects (from -1 to 44 D) 7.1% of 522 (15 subjects with empty value)	n = 20 subjects (from -8 to 24 D) 10.7% of 187 (350 subjects with empty value)	n = 7 subjects (from -8 to 115 D) 1.4% of 500 (37 subjects with empty value)

Notes: W = Weeks D = days
n = number of subjects out of the specified interval
% = proportion of subjects out of the specified interval among with subjects present at the considered visits
% (for age) = proportion of subjects out of the specified interval using as denominator the number of subjects in the considered cohort.
VAC_1 = visit for first dose VAC_2 = visit for second dose
BL_3 = visit for post-vaccination blood sampling at 2 months after the second dose of HRV vaccine or placebo
BL_4 = visit for post-vaccination blood sampling at the end of the first efficacy follow-up period
VIS_2 = second visit VIS_3 = third visit

Supplement 3: Percentage of GE episodes with no available stools results from 2 weeks after Dose 2 up to the end of the first efficacy follow-up period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

	HRV $10^{4.7}$ N'= 411		**HRV $10^{5.2}$ N'= 385**		**HRV $10^{5.8}$ N'= 420**		**Placebo N'= 419**	
Category	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
No stools collected	87	21.2	102	26.5	121	28.8	91	21.7
Stools collected but no results available	8	1.9	7	1.8	4	1.0	4	1.0
No stool results available	95	23.1	109	28.3	125	29.8	95	22.7

Notes: N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category

Supplement 4: Summary of demographic characteristics (age calculated in weeks) (total vaccinated cohort for subset planned to receive two doses of study vaccine)

	Parameters or	HRV_4.7 N= 538		HRV_5.2 N= 540		HRV_5.8 N= 540		Placebo N= 537		Total N= 2155	
Characteristics	**Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at first dose (Weeks)	Mean	8.3	-	8.4	-	8.3	-	8.4	-	8.3	-
	SD	1.52	-	1.50	-	1.51	-	1.58	-	1.50	-
	Median	8	-	8	-	8	-	8	-	8	-
	Minimum	6	-	6	-	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	240	44.6	265	49.1	254	47.0	267	49.7	1026	47.6
	Male	298	55.4	275	50.9	286	53.0	270	50.3	1129	52.4
Race	Black	21	3.9	17	3.1	19	3.5	13	2.4	70	3.2
	White/Caucasian	114	21.2	132	24.4	140	25.9	134	25.0	520	24.1
	Oriental	0	0.0	0	0.0	0	0.0	1	0.2	1	0.0
	Other	403	74.9	391	72.4	381	70.6	389	72.4	1564	72.6
Height(cm)	Mean	57.3	-	57.4	-	57.4	-	57.6	-	57.4	-
	SD	2.78	-	2.66	-	2.90	-	2.92	-	2.80	-
	Median	57	-	57	-	57	-	57	-	57	-
	Unknown	2	-	2	-	1	-	1	-	6	-
Weight(kg)	Mean	5.3	-	5.3	-	5.3	-	5.3	-	5.3	-
	SD	0.75	-	0.69	-	0.76	-	0.76	-	0.70	-
	Median	5.2	-	5.3	-	5.3	-	5.3	-	5.3	-
	Unknown	2	-	0	-	1	-	1	-	4	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

Supplement 5: Summary of demographic characteristics (age calculated in weeks) in Brazil (total vaccinated cohort for subset planned to receive two doses of study vaccine)

	Parameters or	HRV_4.7 N= 194		HRV_5.2 N= 196		HRV_5.8 N= 194		Placebo N= 194		Total N= 778	
Characteristics	**Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at first dose (Weeks)	Mean	8.3	-	8.3	-	8.2	-	8.6	-	8.3	-
	SD	1.85	-	1.84	-	1.74	-	1.98	-	1.90	-
	Median	8	-	8	-	8	-	9	-	8	-
	Minimum	6	-	6	-	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	82	42.3	94	48.0	93	47.9	98	50.5	367	47.2
	Male	112	57.7	102	52.0	101	52.1	96	49.5	411	52.8
Race	Black	14	7.2	10	5.1	11	5.7	8	4.1	43	5.5
	White/Caucasian	21	10.8	35	17.9	24	12.4	36	18.6	116	14.9
	Other	159	82.0	151	77.0	159	82.0	150	77.3	619	79.6
Height(cm)	Mean	56.8	-	57.1	-	56.7	-	57.1	-	56.9	-
	SD	2.51	-	2.51	-	2.90	-	2.85	-	2.70	-
	Median	57	-	57	-	57	-	57	-	57	-
	Unknown	2	-	2	-	1	-	1	-	6	-
Weight(kg)	Mean	5.4	-	5.4	-	5.2	-	5.4	-	5.3	-
	SD	0.83	-	0.77	-	0.74	-	0.79	-	0.80	-
	Median	5.2	-	5.35	-	5.2	-	5.3	-	5.2	-
	Unknown	2	-	0	-	1	-	1	-	4	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

Supplement 6: Summary of demographic characteristics (age calculated in weeks) in Mexico (total vaccinated cohort for subset planned to receive two doses of study vaccine)

	Parameters or	HRV_4.7 N= 101		HRV_5.2 N= 101		HRV_5.8 N= 102		Placebo N= 101		Total N= 405	
Characteristics	**Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at first dose (Weeks)	Mean	7.6	-	7.9	-	7.6	-	7.8	-	7.7	-
	SD	1.37	-	1.49	-	1.59	-	1.51	-	1.50	-
	Median	8	-	8	-	7	-	8	-	8	-
	Minimum	6	-	6	-	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	34	33.7	52	51.5	47	46.1	44	43.6	177	43.7
	Male	67	66.3	49	48.5	55	53.9	57	56.4	228	56.3
Race	Black	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White/Caucasian	6	5.9	5	5.0	5	4.9	2	2.0	18	4.4
	Other	95	94.1	96	95.0	97	95.1	99	98.0	387	95.6
Height(cm)	Mean	55.2	-	55.4	-	55.3	-	55.7	-	55.4	-
	SD	2.23	-	2.07	-	2.39	-	2.42	-	2.30	-
	Median	55	-	55	-	55	-	56	-	55	-
Weight(kg)	Mean	4.9	-	5.0	-	4.9	-	5.0	-	4.9	-
	SD	0.61	-	0.60	-	0.76	-	0.62	-	0.70	-
	Median	5	-	5.1	-	4.8	-	5	-	5	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

Supplement 7: Summary of demographic characteristics (age calculated in weeks) in Venezuela (total vaccinated cohort for subset planned to receive two doses of study vaccine)

	Parameters or	HRV_4.7 N= 243		HRV_5.2 N= 243		HRV_5.8 N= 244		Placebo N= 242		Total N= 972	
Characteristics	**Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at first dose (Weeks)	Mean	8.6	-	8.6	-	8.6	-	8.6	-	8.6	-
	SD	1.16	-	1.12	-	1.14	-	1.11	-	1.10	-
	Median	8	-	8	-	8	-	8	-	8	-
	Minimum	6	-	7	-	7	-	7	-	6	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	124	51.0	119	49.0	114	46.7	125	51.7	482	49.6
	Male	119	49.0	124	51.0	130	53.3	117	48.3	490	50.4
Race	Black	7	2.9	7	2.9	8	3.3	5	2.1	27	2.8
	White/Caucasian	87	35.8	92	37.9	111	45.5	96	39.7	386	39.7
	Oriental	0	0.0	0	0.0	0	0.0	1	0.4	1	0.1
	Other	149	61.3	144	59.3	125	51.2	140	57.9	558	57.4
Height(cm)	Mean	58.5	-	58.5	-	58.8	-	58.8	-	58.6	-
	SD	2.59	-	2.45	-	2.31	-	2.62	-	2.50	-
	Median	59	-	59	-	59	-	59	-	59	-
Weight(kg)	Mean	5.4	-	5.4	-	5.5	-	5.5	-	5.5	-
	SD	0.68	-	0.61	-	0.69	-	0.73	-	0.70	-
	Median	5.4	-	5.4	-	5.5	-	5.5	-	5.4	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

Supplement 8: Increase in height and weight from Visit 1 to Visit 2, 3 and 4 (total vaccinated cohort for subset planned to receive two doses of study vaccine)

Visit	Characteristics	Parameters	HRV_4.7 N = (538)	HRV_5.2 N = (540)	HRV_5.8 N = (540)	Placebo N = (537)	Total N = (2155)
			Value	Value	Value	Value	Value
Visit 2	Increase in height (cm) from Visit 1	Mean	5.8	5.8	5.9	5.7	5.8
		SD	2.42	2.22	2.42	2.58	2.41
		Median	6	6	6	6	6
		Unknown	29	28	27	15	99
	Increase in weight (kg) from Visit 1	Mean	1.6	1.6	1.6	1.5	1.6
		SD	0.55	0.55	0.52	0.54	0.54
		Median	1.5	1.5	1.5	1.5	1.5
		Unknown	29	27	26	15	97
Visit 3	Increase in height (cm) from Visit 1	Mean	9.7	9.3	9.7	9.5	9.6
		SD	2.48	3.87	2.65	2.71	2.98
		Median	10	9	10	9	10
		Unknown	35	36	37	27	135
	Increase in weight (kg) from Visit 1	Mean	2.5	2.5	2.5	2.4	2.5
		SD	0.75	0.68	0.74	0.71	0.72
		Median	2.4	2.4	2.4	2.4	2.4
		Unknown	35	35	37	27	134
Visit 4	Increase in height (cm) from Visit 1	Mean	17.3	17.1	17.1	17	17.1
		SD	2.83	2.74	2.69	2.81	2.77
		Median	17	17	17	17	17
		Unknown	43	43	44	33	163
	Increase in weight (kg) from Visit 1	Mean	4.0	4.0	4.0	4.0	4.0
		SD	0.97	0.87	0.98	0.9	0.93
		Median	4	3.9	3.9	3.9	3.9
		Unknown	41	42	42	37	162

Notes: N = Total number of subjects by group or in total (sum of all groups)
Value = value of the considered parameter
SD = standard deviation

Supplement 9: Summary of demographic characteristics (age calculated in weeks) (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

	Parameters or	HRV_4.7 N= 395		HRV_5.2 N= 377		HRV_5.8 N= 381		Placebo N= 373		Total N= 1526	
Characteristics	**Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at first dose (Weeks)	Mean	8.2	-	8.4	-	8.3	-	8.3	-	8.3	-
	SD	1.49	-	1.44	-	1.45	-	1.48	-	1.50	-
	Median	8	-	8	-	8	-	8	-	8	-
	Minimum	6	-	6	-	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	182	46.1	195	51.7	180	47.2	186	49.9	743	48.7
	Male	213	53.9	182	48.3	201	52.8	187	50.1	783	51.3
Race	Black	18	4.6	10	2.7	13	3.4	10	2.7	51	3.3
	White/Caucasian	80	20.3	96	25.5	104	27.3	95	25.5	375	24.6
	Other	297	75.2	271	71.9	264	69.3	268	71.8	1100	72.1
Height(cm)	Mean	57.2	-	57.4	-	57.6	-	57.6	-	57.5	-
	SD	2.79	-	2.53	-	2.87	-	2.83	-	2.80	-
	Median	57	-	57	-	58	-	58	-	57	-
	Unknown	1	-	1	-	0	-	1	-	3	-
Weight(kg)	Mean	5.3	-	5.3	-	5.3	-	5.3	-	5.3	-
	SD	0.74	-	0.65	-	0.73	-	0.75	-	0.70	-
	Median	5.2	-	5.3	-	5.3	-	5.3	-	5.3	-
	Unknown	2	-	0	-	1	-	0	-	3	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

Supplement 10: Percentage of subjects who received OPV at birth (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

HRV_4.7			HRV_5.2			HRV_5.8			Placebo		
N	n	%	N	n	%	N	n	%	N	n	%
395	54	13.7	377	61	16.2	381	45	11.8	373	59	15.8

Notes: N = Number of subjects in the considered cohort
n/% = number/percentage of subjects with OPV given at birth

Supplement 11: Summary of feeding criteria (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Dose	Group	N	Feeding criteria					
			Breast milk		Infant formula		Both	
			n	%	n	%	n	%
1	HRV_4.7	395	218	55.2	14	3.5	163	41.3
	HRV_5.2	377	192	50.9	15	4.0	170	45.1
	HRV_5.8	381	212	55.6	16	4.2	153	40.2
	Placebo	373	214	57.4	14	3.8	145	38.9
2	HRV_4.7	388	176	45.4	32	8.2	180	46.4
	HRV_5.2	369	171	46.3	36	9.8	162	43.9
	HRV_5.8	371	160	43.1	42	11.3	169	45.6
	Placebo	372	182	48.9	37	9.9	153	41.1

Notes: N = number of subjects having received the considered dose and with available data
n/% = number/percentage of subjects with the specified feeding criteria

Supplement 12: Duration (in years) of the follow-up period from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Duration (years) Of follow-up period	HRV $10^{4.7}$ N= 468	HRV $10^{5.2}$ N= 460	HRV $10^{5.8}$ N= 464	Placebo N= 454
Total	282.6	276.5	277.8	271.9
Mean	0.604	0.601	0.599	0.599
Minimum	0.115	0.027	0.003	0.016
Q1	0.567	0.566	0.567	0.564
Median	0.595	0.597	0.597	0.595
Q3	0.649	0.640	0.641	0.638
Maximum	1.025	0.841	1.027	0.767

Notes: N = number of subjects included in each group
Total = sum of follow-up period expressed in year
Q1 = 25th percentile
Q3 = 75th percentile

Supplement 13: Percentage of subjects who reported GE episode(s) from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Event	Total number of episode reported	HRV $10^{4.7}$ N= 468		HRV $10^{5.2}$ N= 460		HRV $10^{5.8}$ N= 464		Placebo N= 454	
		n	%	n	%	n	%	n	%
GE	**1**	87	18.6	84	18.3	83	17.9	109	24.0
	2	54	11.5	45	9.8	55	11.9	44	9.7
	3	27	5.8	26	5.7	31	6.7	37	8.1
	4	15	3.2	12	2.6	10	2.2	14	3.1
	5	11	2.4	5	1.1	9	1.9	6	1.3
	6	2	0.4	4	0.9	1	0.2	3	0.7
	7	0	0.0	4	0.9	5	1.1	1	0.2
	8	1	0.2	1	0.2	1	0.2	0	0.0
	Any	197	42.1	181	39.3	195	42.0	214	47.1
RV GE	**1**	21	4.5	22	4.8	15	3.2	47	10.4
	2	0	0.0	0	0.0	0	0.0	2	0.4
	Any	21	4.5	22	4.8	15	3.2	49	10.8

Notes:
N = number of subjects included in each group
n/% = number/percentage of subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified symptom

Supplement 14: Characteristics of GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 411		HRV $10^{5.2}$ N'= 385		HRV $10^{5.8}$ N'= 420		Placebo N'= 419	
		Value or n	Value or n	Value or n	Value or n	Value or n	Value or n	Value or n	Value or n
Severity Score	**Mean**	7.64	-	7.01	-	7.00	-	8.03	-
	SD	4.05	-	3.84	-	3.75	-	4.24	-
	Median	7.00	-	6.00	-	6.00	-	7.00	-
	Minimum	2.00	-	2.00	-	2.00	-	2.00	-
	Maximum	20.00	-	20.00	-	20.00	-	20.00	-
Duration of looser than Normal stools (days)	**1-4 days**	253	61.6	246	63.9	265	63.1	255	60.9
	5 days	30	7.3	32	8.3	36	8.6	32	7.6
	≥ 6 days	128	31.1	107	27.8	119	28.3	132	31.5
Maximum number of looser Than normal stools/24 hours	**1-3**	67	16.3	73	19.0	86	20.5	72	17.2
	4-5	184	44.8	181	47.0	192	45.7	176	42.0
	≥ 6	160	38.9	131	34.0	142	33.8	171	40.8
Duration of vomiting	**0 day**	238	57.9	234	60.8	260	61.9	225	53.7
	1 day	77	18.7	77	20.0	83	19.8	89	21.2
	2 days	36	8.8	33	8.6	40	9.5	43	10.3
	≥ 3 days	60	14.6	41	10.6	37	8.8	62	14.8
Maximum number of Episodes of Vomiting/24 hours	**0**	238	57.9	234	60.8	260	61.9	225	53.7
	1	47	11.4	37	9.6	60	14.3	40	9.5
	2	90	21.9	93	24.2	78	18.6	107	25.5
	≥ 3	36	8.8	21	5.5	22	5.2	47	11.2
Maximum fever reported /24 hours (measured rectally)	**< 37.1°C**	178	43.3	220	57.1	217	51.7	199	47.5
	37.1-38.4°C	128	31.1	91	23.6	103	24.5	108	25.8
	38.5-38.9°C	36	8.8	27	7.0	37	8.8	34	8.1
	≥ 39°C	69	16.8	47	12.2	63	15.0	78	18.6
Treatment	**none**	127	30.9	131	34.0	144	34.3	109	26.0
	Rehydration	263	64.0	239	62.1	259	61.7	282	67.3
	Hospitalisation	21	5.1	15	3.9	17	4.0	28	6.7
Dehydration	**none**	342	83.2	323	83.9	359	85.5	326	77.8
	1-5%	56	13.6	52	13.5	48	11.4	72	17.2
	≥ 6%	13	3.2	10	2.6	13	3.1	21	5.0

Notes: N' = number of GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 15: Characteristics of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 21		HRV $10^{5.2}$ N'= 22		HRV $10^{5.8}$ N'= 15		Placebo N'= 51	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	**Mean**	11.05	-	8.82	-	9.27	-	12.35	-
	SD	4.36	-	4.37	-	3.47	-	4.40	-
	Median	11.00	-	8.00	-	9.00	-	13.00	-
	Minimum	3.00	-	2.00	-	3.00	-	2.00	-
	Maximum	18.00	-	16.00	-	16.00	-	20.00	-
Duration of looser than Normal stools (days)	**1-4 days**	14	66.7	13	59.1	10	66.7	26	51.0
	5 days	5	23.8	4	18.2	0	0.0	12	23.5
	≥ 6 days	2	9.5	5	22.7	5	33.3	13	25.5
Maximum number of looser than normal stools /24 hours	**1-3**	1	4.8	3	13.6	2	13.3	7	13.7
	4-5	7	33.3	9	40.9	7	46.7	10	19.6
	≥ 6	13	61.9	10	45.5	6	40.0	34	66.7
Duration of vomiting	**0 day**	4	19.0	9	40.9	7	46.7	6	11.8
	1 day	8	38.1	4	18.2	3	20.0	14	27.5
	2 days	2	9.5	4	18.2	3	20.0	10	19.6
	≥ 3 days	7	33.3	5	22.7	2	13.3	21	41.2
Maximum number of Episodes of Vomiting/24 hours	**0**	4	19.0	9	40.9	7	46.7	6	11.8
	1	3	14.3	1	4.5	0	0.0	5	9.8
	2	9	42.9	11	50.0	8	53.3	21	41.2
	≥ 3	5	23.8	1	4.5	0	0.0	19	37.3
Maximum fever reported /24 hours (measured rectally)	**< 37.1°C**	4	19.0	15	68.2	3	20.0	7	13.7
	37.1-38.4°C	5	23.8	1	4.5	5	33.3	14	27.5
	38.5-38.9°C	7	33.3	2	9.1	2	13.3	11	21.6
	≥ 39°C	5	23.8	4	18.2	5	33.3	19	37.3
Treatment	**none**	3	14.3	3	13.6	3	20.0	4	7.8
	Rehydration	13	61.9	18	81.8	9	60.0	33	64.7
	Hospitalisation	5	23.8	1	4.5	3	20.0	14	27.5
Dehydration	**none**	11	52.4	14	63.6	11	73.3	27	52.9
	1-5%	8	38.1	7	31.8	2	13.3	15	29.4
	≥ 6%	2	9.5	1	4.5	2	13.3	9	17.6

Notes: N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 16: Characteristics of RV GE episodes of G1 wild type, reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 12		HRV $10^{5.2}$ N'= 6		HRV $10^{5.8}$ N'= 7		Placebo N'= 30	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	**Mean**	10.08	-	10.50	-	9.00	-	10.80	-
	SD	4.19	-	2.88	-	2.77	-	3.98	-
	Median	11.00	-	11.50	-	10.00	-	11.00	-
	Minimum	3.00	-	7.00	-	3.00	-	2.00	-
	Maximum	15.00	-	14.00	-	11.00	-	18.00	-
Duration of looser than Normal stools (days)	**1-4 days**	10	83.3	6	100.0	5	71.4	19	63.3
	5 days	2	16.7	0	0.0	0	0.0	7	23.3
	≥ 6 days	0	0.0	0	0.0	2	28.6	4	13.3
Maximum number of looser than normal stools /24 hours	**1-3**	1	8.3	0	0.0	1	14.3	5	16.7
	4-5	4	33.3	2	33.3	2	28.6	7	23.3
	≥ 6	7	58.3	4	66.7	4	57.1	18	60.0
Duration of vomiting	**0 day**	3	25.0	1	16.7	4	57.1	5	16.7
	1 day	5	41.7	1	16.7	2	28.6	9	30.0
	2 days	1	8.3	1	16.7	1	14.3	6	20.0
	≥ 3 days	3	25.0	3	50.0	0	0.0	10	33.3
Maximum number of episodes of vomiting/24 hours	**0**	3	25.0	1	16.7	4	57.1	5	16.7
	1	2	16.7	0	0.0	0	0.0	5	16.7
	2	5	41.7	4	66.7	3	42.9	9	30.0
	≥ 3	2	16.7	1	16.7	0	0.0	11	36.7
Maximum fever reported /24 hours (measured rectally)	**< 37.1°C**	2	16.7	3	50.0	1	14.3	5	16.7
	37.1-38.4°C	3	25.0	0	0.0	1	14.3	8	26.7
	38.5-38.9°C	4	33.3	2	33.3	1	14.3	6	20.0
	≥ 39°C	3	25.0	1	16.7	4	57.1	11	36.7
Treatment	**none**	2	16.7	1	16.7	1	14.3	4	13.3
	Rehydration	8	66.7	5	83.3	5	71.4	24	80.0
	Hospitalisation	2	16.7	0	0.0	1	14.3	2	6.7
Dehydration	**none**	7	58.3	3	50.0	6	85.7	21	70.0
	1-5%	4	33.3	3	50.0	0	0.0	9	30.0
	≥ 6%	1	8.3	0	0.0	1	14.3	0	0.0

Notes: N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 17: Characteristics of RV GE episodes of G9 type, reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 8		HRV $10^{5.2}$ N'= 14		HRV $10^{5.8}$ N'= 6		Placebo N'= 15	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	**Mean**	11.63	-	8.79	-	10.17	-	14.87	-
	SD	4.24	-	4.76	-	4.71	-	4.00	-
	Median	11.50	-	8.00	-	9.50	-	16.00	-
	Minimum	6.00	-	2.00	-	4.00	-	6.00	-
	Maximum	17.00	-	16.00	-	16.00	-	20.00	-
Duration of looser than Normal stools (days)	**1-4 days**	3	37.5	5	35.7	4	66.7	3	20.0
	5 days	3	37.5	4	28.6	0	0.0	5	33.3
	≥ 6 days	2	25.0	5	35.7	2	33.3	7	46.7
Maximum number of looser than normal stools /24 hours	**1-3**	0	0.0	2	14.3	1	16.7	1	6.7
	4-5	3	37.5	7	50.0	3	50.0	2	13.3
	≥ 6	5	62.5	5	35.7	2	33.3	12	80.0
Duration of vomiting	**0 day**	1	12.5	6	42.9	2	33.3	1	6.7
	1 day	3	37.5	3	21.4	1	16.7	3	20.0
	2 days	1	12.5	3	21.4	1	16.7	3	20.0
	≥ 3 days	3	37.5	2	14.3	2	33.3	8	53.3
Maximum number of Episodes of Vomiting/24 hours	**0**	1	12.5	6	42.9	2	33.3	1	6.7
	1	1	12.5	1	7.1	0	0.0	0	0.0
	2	4	50.0	7	50.0	4	66.7	8	53.3
	≥ 3	2	25.0	0	0.0	0	0.0	6	40.0
Maximum fever reported /24 hours (measured rectally)	**< 37.1°C**	2	25.0	10	71.4	2	33.3	2	13.3
	37.1-38.4°C	2	25.0	1	7.1	2	33.3	5	33.3
	38.5-38.9°C	3	37.5	0	0.0	1	16.7	4	26.7
	≥ 39°C	1	12.5	3	21.4	1	16.7	4	26.7
Treatment	**none**	1	12.5	2	14.3	1	16.7	0	0.0
	Rehydration	5	62.5	11	78.6	3	50.0	5	33.3
	Hospitalisation	2	25.0	1	7.1	2	33.3	10	66.7
Dehydration	**none**	4	50.0	9	64.3	3	50.0	3	20.0
	1-5%	4	50.0	4	28.6	2	33.3	5	33.3
	≥ 6%	0	0.0	1	7.1	1	16.7	7	46.7

Notes: N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 18: Percentage of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period, by mixed infection (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

	HRV $10^{4.7}$ N'= 21		HRV $10^{5.2}$ N'= 22		HRV $10^{5.8}$ N'= 15		Placebo N'= 51	
Mixed infection	**n**	**%**	**n**	**%**	**n**	**%**	**N**	**%**
At least one mixed infection	1	4.8	0	0.0	2	13.3	3	5.9
Campylobacter	0	0.0	0	0.0	0	0.0	0	0.0
Salmonella	1	4.8	0	0.0	0	0.0	0	0.0
Shigella	0	0.0	0	0.0	1	6.7	1	2.0
Ag-E.Coli	0	0.0	0	0.0	0	0.0	0	0.0
ETEC	0	0.0	0	0.0	0	0.0	0	0.0
EPEC	0	0.0	0	0.0	0	0.0	1	2.0
EAgEC	0	0.0	0	0.0	1	6.7	1	2.0
EIEC	0	0.0	0	0.0	0	0.0	0	0.0

Notes: N'= number of RV GE episodes reported
n/% = number/percentage of mixed RV GE episodes reported in each group, among all RV GE episodes reported in the first efficacy follow-up period

Supplement 19: Percentage of vaccinees reporting RV GE episodes from 2 weeks after Dose 2 up to the end of the first efficacy period, by status of anti-rotavirus IgA antibody concentration at two months after Dose 2 (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Anti-rotavirus	HRV $10^{4.7}$					HRV $10^{5.2}$				
Antibody status				**95%CI**					**95%CI**	
At Visit 3	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Negative	64	7	10.9	4.5	21.3	52	6	11.5	4.4	23.4
Positive	103	1	1.0	0.0	5.3	100	2	2.0	0.2	7.0
Unknown	301	13	4.3	2.3	7.3	308	14	4.5	2.5	7.5

Anti-rotavirus	HRV $10^{5.8}$					Pooled HRV groups				
Antibody status				**95%CI**					**95%CI**	
At Visit 3	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Negative	53	6	11.3	4.3	23.0	169	19	11.2	6.9	17.0
Positive	106	2	1.9	0.2	6.7	309	5	1.6	0.5	3.7
Unknown	305	7	2.3	0.9	4.7	914	34	3.7	2.6	5.2

Notes: N = number of subjects included in the vaccine group with the specified status for anti-rotavirus IgA antibody concentration two months after Dose 2
n/% = number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration two months after Dose 2 reporting at least one RV GE episode from 2 weeks after Dose 2 up to the end of the first efficacy period
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 20: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Group	N	n	T (year)	n/T value	95%CI LL	95%CI UL	n/N %	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	p-value
G1 wild type													
HRV $10^{4.7}$	468	12	279.1	0.043	0.024	0.076	2.6	1.3	4.4	59.9	18.9	81.3	0.006
HRV $10^{5.2}$	460	6	274.7	0.022	0.010	0.049	1.3	0.5	2.8	79.6	49.9	93.1	<0.001
HRV $10^{5.8}$	464	7	275.3	0.025	0.012	0.053	1.5	0.6	3.1	76.4	44.9	91.3	<0.001
Pooled HRV Groups	1392	25	829.1	0.030	0.020	0.045	1.8	1.2	2.6	71.9	50.3	84.2	<0.001
Placebo	454	29	263.0	0.110	0.077	0.159	6.4	4.3	9.0	-	-	-	-
G9													
HRV $10^{4.7}$	468	8	279.9	0.029	0.014	0.057	1.7	0.7	3.3	48.3	-30.0	81.0	0.141
HRV $10^{5.2}$	460	14	271.0	0.052	0.031	0.087	3.0	1.7	5.1	7.9	-105	58.8	0.852
HRV $10^{5.8}$	464	7	275.4	0.025	0.012	0.053	1.5	0.6	3.1	54.3	-19.0	84.3	0.086
Pooled HRV Groups	1392	29	826.2	0.035	0.024	0.051	2.1	1.4	3.0	36.9	-26.5	67.3	0.156
Placebo	454	15	266.5	0.056	0.034	0.093	3.3	1.9	5.4	-	-	-	-
Pooled Non G1 (G2, G3, G4, G9)													
HRV $10^{4.7}$	468	9	279.8	0.032	0.017	0.062	1.9	0.9	3.6	56.3	-0.3	82.5	0.037
HRV $10^{5.2}$	460	14	271.0	0.052	0.031	0.087	3.0	1.7	5.1	30.9	-43.8	67.7	0.299
HRV $10^{5.8}$	464	8	274.7	0.029	0.015	0.058	1.7	0.7	3.4	60.9	7.2	85.1	0.021
Pooled HRV Groups	1392	31	825.5	0.038	0.026	0.053	2.2	1.5	3.1	49.4	6.4	72.1	0.020
Placebo	454	20	265.6	0.075	0.049	0.117	4.4	2.7	6.7	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one RV GE episode in each group
n/T= person-year rate of RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 21: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
G1 wild type													
HRV $10^{4.7}$	468	7	280.7	0.025	0.012	0.052	1.5	0.6	3.1	57.6	-9.0	85.2	0.057
HRV $10^{5.2}$	460	4	275.4	0.015	0.005	0.039	0.9	0.2	2.2	75.3	23.5	94.0	0.006
HRV $10^{5.8}$	464	2	276.9	0.007	0.002	0.029	0.4	0.1	1.5	87.8	48.0	98.6	<0.001
Pooled HRV Groups	1392	13	833.0	0.016	0.009	0.027	0.9	0.5	1.6	73.5	41.2	88.3	<0.001
Placebo	454	16	267.2	0.060	0.037	0.098	3.5	2.0	5.7	-	-	-	-
G9													
HRV $10^{4.7}$	468	4	281.6	0.014	0.005	0.038	0.9	0.2	2.2	70.2	3.4	92.9	0.027
HRV $10^{5.2}$	460	6	274.3	0.022	0.010	0.049	1.3	0.5	2.8	54.4	-28.5	85.8	0.109
HRV $10^{5.8}$	464	3	277.0	0.011	0.003	0.034	0.6	0.1	1.9	77.4	17.8	95.9	0.011
Pooled HRV Groups	1392	13	832.8	0.016	0.009	0.027	0.9	0.5	1.6	67.4	23.6	86.1	0.005
Placebo	454	13	267.6	0.049	0.028	0.084	2.9	1.5	4.8	-	-	-	-
Pooled Non G1 (G2, G3, G4, G9)													
HRV $10^{4.7}$	468	5	281.5	0.018	0.007	0.043	1.1	0.3	2.5	71.5	19.4	91.8	0.009
HRV $10^{5.2}$	460	6	274.3	0.022	0.010	0.049	1.3	0.5	2.8	65.2	7.4	88.8	0.020
HRV $10^{5.8}$	464	3	277.0	0.011	0.003	0.034	0.6	0.1	1.9	82.7	40.3	96.8	0.001
Pooled HRV Groups	1392	14	832.8	0.017	0.010	0.028	1.0	0.6	1.7	73.1	42.1	87.7	<0.001
Placebo	454	17	266.7	0.064	0.040	0.103	3.7	2.2	5.9	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T= sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 22: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**p-value**
Brazil													
HRV $10^{4.7}$	163	16	101.7	0.157	0.096	0.257	9.8	5.7	15.5	39.1	-19.6	69.7	0.127
HRV $10^{5.2}$	153	18	93.5	0.193	0.121	0.306	11.8	7.1	18.0	27.0	-40.4	62.7	0.320
HRV $10^{5.8}$	170	10	107.1	0.093	0.050	0.173	5.9	2.9	10.6	63.5	20.8	84.4	0.004
Pooled HRV Groups	486	44	302.3	0.146	0.108	0.196	9.1	6.7	12.0	43.8	3.4	66.6	0.022
Placebo	149	24	89.8	0.267	0.179	0.399	16.1	10.6	23.0	-	-	-	-
Mexico													
HRV $10^{4.7}$	79	1	46.5	0.022	0.003	0.153	1.3	0.0	6.9	90.8	38.0	99.8	0.003
HRV $10^{5.2}$	86	3	48.8	0.061	0.020	0.191	3.5	0.7	9.9	74.7	6.3	95.4	0.028
HRV $10^{5.8}$	78	3	43.7	0.069	0.022	0.213	3.8	0.8	10.8	72.1	-3.3	95.0	0.031
Pooled HRV Groups	243	7	139.0	0.050	0.024	0.106	2.9	1.2	5.8	79.1	42.5	93.0	<0.001
Placebo	87	12	46.4	0.259	0.147	0.456	13.8	7.3	22.9	-	-	-	-
Venezuela													
HRV $10^{4.7}$	226	4	128.3	0.031	0.012	0.083	1.8	0.5	4.5	70.3	3.9	93.0	0.026
HRV $10^{5.2}$	221	1	126.1	0.008	0.001	0.056	0.5	0.0	2.5	92.4	49.5	99.8	<0.001
HRV $10^{5.8}$	216	2	121.4	0.016	0.004	0.066	0.9	0.1	3.3	84.5	31.4	98.3	0.006
Pooled HRV Groups	663	7	375.8	0.019	0.009	0.039	1.1	0.4	2.2	82.3	52.3	94.0	<0.001
Placebo	218	13	120.3	0.108	0.063	0.186	6.0	3.2	10.0	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one RV GE episode in each group
n/T = person-year rate of RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 23: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
Brazil													
HRV $10^{4.7}$	163	9	104.3	0.086	0.045	0.166	5.5	2.6	10.2	56.7	-0.4	82.7	0.030
HRV $10^{5.2}$	153	9	97.2	0.093	0.048	0.178	5.9	2.7	10.9	53.9	-7.0	81.6	0.047
HRV $10^{5.8}$	170	4	109.1	0.037	0.014	0.098	2.4	0.6	5.9	81.5	44.5	95.4	<0.001
Pooled HRV Groups	486	22	310.6	0.071	0.047	0.108	4.5	2.9	6.8	64.5	30.7	81.7	<0.001
Placebo	149	19	91.2	0.208	0.133	0.327	12.8	7.9	19.2	-	-	-	-
Mexico													
HRV $10^{4.7}$	79	1	46.5	0.022	0.003	0.153	1.3	0.0	6.9	84.3	-22.5	99.7	0.066
HRV $10^{5.2}$	86	0	49.8	0.000	Und.	Und.	0.0	0.0	4.2	100.0	29.8	100.0	0.014
HRV $10^{5.8}$	78	0	45.2	0.000	Und.	Und.	0.0	0.0	4.6	100.0	22.6	100.0	0.015
Pooled HRV Groups	243	1	141.5	0.007	0.001	0.050	0.4	0.0	2.3	94.9	60.2	99.9	<0.001
Placebo	87	7	48.4	0.145	0.069	0.304	8.0	3.3	15.9	-	-	-	-
Venezuela													
HRV $10^{4.7}$	226	2	128.9	0.016	0.004	0.062	0.9	0.1	3.2	75.9	-20.8	97.5	0.058
HRV $10^{5.2}$	221	1	126.1	0.008	0.001	0.056	0.5	0.0	2.5	87.7	8.0	99.7	0.020
HRV $10^{5.8}$	216	1	121.7	0.008	0.001	0.058	0.5	0.0	2.6	87.4	5.9	99.7	0.037
Pooled HRV Groups	663	4	376.8	0.011	0.004	0.028	0.6	0.2	1.5	83.6	38.6	96.4	0.002
Placebo	218	8	122.2	0.065	0.033	0.131	3.7	1.6	7.1	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
und = cannot be estimate
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 24: Duration (in years) of the follow-up period from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Duration (years) of follow-up period	**HRV $10^{4.7}$ N= 507**	**HRV $10^{5.2}$ N= 508**	**HRV $10^{5.8}$ N= 512**	**Placebo N= 517**
Total	306.8	305.9	307.3	310.6
Mean	0.605	0.602	0.600	0.601
Minimum	0.115	0.027	0.003	0.016
Q1	0.567	0.567	0.567	0.567
Median	0.600	0.597	0.599	0.597
Q3	0.652	0.641	0.641	0.638
Maximum	1.025	0.841	1.027	1.030

Notes: N = number of subjects included in each group
Total = sum of follow-up period expressed in year
Q1 = 25th percentile
Q3 = 75th percentile

Supplement 25: Percentage of subjects who reported GE episode(s) from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Event	Total number of episode reported	HRV $10^{4.7}$ N= 507		HRV $10^{5.2}$ N= 508		HRV $10^{5.8}$ N= 512		Placebo N= 517	
		n	%	n	%	n	%	n	%
GE	**1**	96	18.9	96	18.9	95	18.6	124	24.0
	2	58	11.4	53	10.4	60	11.7	53	10.3
	3	32	6.3	33	6.5	37	7.2	43	8.3
	4	19	3.7	14	2.8	13	2.5	16	3.1
	5	11	2.2	5	1.0	11	2.1	12	2.3
	6	2	0.4	4	0.8	2	0.4	3	0.6
	7	0	0.0	5	1.0	6	1.2	1	0.2
	8	2	0.4	1	0.2	1	0.2	1	0.2
	Any	220	43.4	211	41.5	225	43.9	253	48.9
RV GE	**1**	22	4.3	22	4.3	15	2.9	53	10.3
	2	0	0.0	0	0.0	0	0.0	2	0.4
	Any	22	4.3	22	4.3	15	2.9	55	10.6

Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified symptom

Supplement 26: Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period, by severity (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Event	Severity	HRV $10^{4.7}$		HRV $10^{5.2}$		HRV $10^{5.8}$		Placebo	
		n	%	n	%	n	%	n	%
Any GE	**Mild (1-6)**	224	48.0	228	50.8	263	53.1	231	44.8
	Moderate (7-10)	141	30.2	136	30.3	149	30.1	153	29.7
	Severe (≥11)	102	21.8	85	18.9	83	16.8	132	25.6
	Any	467	100	449	100	495	100	516	100
RV GE	**Mild (1-6)**	4	18.2	8	36.4	2	13.3	5	8.8
	Moderate (7-10)	5	22.7	4	18.2	8	53.3	12	21.1
	Severe (≥11)	13	59.1	10	45.5	5	33.3	40	70.2
	Any	22	100	22	100	15	100	57	100

Notes: n/%= number/percentage of GE episodes reported in each group, by severity, among all GE episodes reported in the first efficacy follow-up period
Any = any specified symptom, regardless of severity

Supplement 27: Percentage of subjects with RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Serotype	HRV $10^{4.7}$ N= 507		HRV $10^{5.2}$ N= 508		HRV $10^{5.8}$ N= 512		Placebo N= 517	
	n	%	n	%	n	%	n	%
Any	22	4.3	22	4.3	15	2.9	55	10.6
G1 wild type	13	2.6	6	1.2	7	1.4	31	6.0
G2	0	0.0	0	0.0	1	0.2	3	0.6
G3	1	0.2	0	0.0	0	0.0	2	0.4
G4	0	0.0	0	0.0	1	0.2	0	0.0
G9	8	1.6	14	2.8	7	1.4	19	3.7
Canine	0	0.0	0	0.0	0	0.0	1	0.2
Unknown	0	0.0	2	0.4	0	0.0	0	0.0

Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified serotype in each group
Any = number of subjects reporting at least one RV GE episode, whatever the serotype

Supplement 28: Characteristics of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 22		HRV $10^{5.2}$ N'= 22		HRV $10^{5.8}$ N'= 15		Placebo N'= 57	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	Mean	11.18	-	8.82	-	9.27	-	12.53	-
	SD	4.31	-	4.37	-	3.47	-	4.27	-
	Median	12.00	-	8.00	-	9.00	-	13.00	-
	Minimum	3.00	-	2.00	-	3.00	-	2.00	-
	Maximum	18.00	-	16.00	-	16.00	-	20.00	-
Duration of looser than Normal stools (days)	1-4 days	14	63.6	13	59.1	10	66.7	28	49.1
	5 days	6	27.3	4	18.2	0	0.0	13	22.8
	≥ 6 days	2	9.1	5	22.7	5	33.3	16	28.1
Maximum number of looser than normal stools/24 hours	1-3	1	4.5	3	13.6	2	13.3	7	12.3
	4-5	8	36.4	9	40.9	7	46.7	12	21.1
	≥ 6	13	59.1	10	45.5	6	40.0	38	66.7
Duration of vomiting	0 day	4	18.2	9	40.9	7	46.7	6	10.5
	1 day	8	36.4	4	18.2	3	20.0	15	26.3
	2 days	2	9.1	4	18.2	3	20.0	11	19.3
	≥ 3 days	8	36.4	5	22.7	2	13.3	25	43.9
Maximum number of episodes of vomiting/24 hours	0	4	18.2	9	40.9	7	46.7	6	10.5
	1	3	13.6	1	4.5	0	0.0	5	8.8
	2	9	40.9	11	50.0	8	53.3	25	43.9
	≥ 3	6	27.3	1	4.5	0	0.0	21	36.8
Maximum fever reported /24 hours (measured rectally)	< 37.1°C	4	18.2	15	68.2	3	20.0	8	14.0
	37.1-38.4°C	5	22.7	1	4.5	5	33.3	16	28.1
	38.5-38.9°C	7	31.8	2	9.1	2	13.3	12	21.1
	≥ 39°C	6	27.3	4	18.2	5	33.3	21	36.8
Treatment	none	3	13.6	3	13.6	3	20.0	4	7.0
	Rehydration	14	63.6	18	81.8	9	60.0	37	64.9
	Hospitalisation	5	22.7	1	4.5	3	20.0	16	28.1
Dehydration	none	12	54.5	14	63.6	11	73.3	29	50.9
	1-5%	8	36.4	7	31.8	2	13.3	19	33.3
	≥ 6%	2	9.1	1	4.5	2	13.3	9	15.8

Notes: N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 29: Characteristics of RV GE episodes of G1 wild type, reported from 2 weeks after Dose 2 stools up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 13		HRV $10^{5.2}$ N'= 6		HRV $10^{5.8}$ N'= 7		Placebo N'= 32	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	Mean	10.38	-	10.50	-	9.00	-	10.88	-
	SD	4.15	-	2.88	-	2.77	-	3.86	-
	Median	11.00	-	11.50	-	10.00	-	11.00	-
	Minimum	3.00	-	7.00	-	3.00	-	2.00	-
	Maximum	15.00	-	14.00	-	11.00	-	18.00	-
Duration of looser than Normal stools (days)	1-4 days	10	76.9	6	100.0	5	71.4	19	59.4
	5 days	3	23.1	0	0.0	0	0.0	8	25.0
	≥ 6 days	0	0.0	0	0.0	2	28.6	5	15.6
Maximum number of looser than normal stools/24 hours	1-3	1	7.7	0	0.0	1	14.3	5	15.6
	4-5	5	38.5	2	33.3	2	28.6	8	25.0
	≥ 6	7	53.8	4	66.7	4	57.1	19	59.4
Duration of vomiting	0 day	3	23.1	1	16.7	4	57.1	5	15.6
	1 day	5	38.5	1	16.7	2	28.6	9	28.1
	2 days	1	7.7	1	16.7	1	14.3	7	21.9
	≥ 3 days	4	30.8	3	50.0	0	0.0	11	34.4
Maximum number of episodes of vomiting/24 hours	0	3	23.1	1	16.7	4	57.1	5	15.6
	1	2	15.4	0	0.0	0	0.0	5	15.6
	2	5	38.5	4	66.7	3	42.9	11	34.4
	≥ 3	3	23.1	1	16.7	0	0.0	11	34.4
Maximum fever reported /24 hours (measured rectally)	< 37.1°C	2	15.4	3	50.0	1	14.3	5	15.6
	37.1-38.4°C	3	23.1	0	0.0	1	14.3	9	28.1
	38.5-38.9°C	4	30.8	2	33.3	1	14.3	7	21.9
	≥ 39°C	4	30.8	1	16.7	4	57.1	11	34.4
Treatment	none	2	15.4	1	16.7	1	14.3	4	12.5
	Rehydration	9	69.2	5	83.3	5	71.4	26	81.3
	Hospitalisation	2	15.4	0	0.0	1	14.3	2	6.3
Dehydration	none	8	61.5	3	50.0	6	85.7	23	71.9
	1-5%	4	30.8	3	50.0	0	0.0	9	28.1
	≥ 6%	1	7.7	0	0.0	1	14.3	0	0.0

Notes: N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 30: Characteristics of RV GE episodes of G9 type, reported from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 8		HRV $10^{5.2}$ N'= 14		HRV $10^{5.8}$ N'= 6		Placebo N'= 19	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	Mean	11.63	-	8.79	-	10.17	-	14.89	-
	SD	4.24	-	4.76	-	4.71	-	3.73	-
	Median	11.50	-	8.00	-	9.50	-	15.00	-
	Minimum	6.00	-	2.00	-	4.00	-	6.00	-
	Maximum	17.00	-	16.00	-	16.00	-	20.00	-
Duration of looser than Normal stools (days)	1-4 days	3	37.5	5	35.7	4	66.7	5	26.3
	5 days	3	37.5	4	28.6	0	0.0	5	26.3
	≥ 6 days	2	25.0	5	35.7	2	33.3	9	47.4
Maximum number of looser than normal stools/24 hours	1-3	0	0.0	2	14.3	1	16.7	1	5.3
	4-5	3	37.5	7	50.0	3	50.0	3	15.8
	≥ 6	5	62.5	5	35.7	2	33.3	15	78.9
Duration of vomiting	0 day	1	12.5	6	42.9	2	33.3	1	5.3
	1 day	3	37.5	3	21.4	1	16.7	4	21.1
	2 days	1	12.5	3	21.4	1	16.7	3	15.8
	≥ 3 days	3	37.5	2	14.3	2	33.3	11	57.9
Maximum number of episodes of vomiting/24 hours	0	1	12.5	6	42.9	2	33.3	1	5.3
	1	1	12.5	1	7.1	0	0.0	0	0.0
	2	4	50.0	7	50.0	4	66.7	10	52.6
	≥ 3	2	25.0	0	0.0	0	0.0	8	42.1
Maximum fever reported /24 hours (measured rectally)	< 37.1°C	2	25.0	10	71.4	2	33.3	3	15.8
	37.1-38.4°C	2	25.0	1	7.1	2	33.3	6	31.6
	38.5-38.9°C	3	37.5	0	0.0	1	16.7	4	21.1
	≥ 39°C	1	12.5	3	21.4	1	16.7	6	31.6
Treatment	none	1	12.5	2	14.3	1	16.7	0	0.0
	Rehydration	5	62.5	11	78.6	3	50.0	7	36.8
	Hospitalisation	2	25.0	1	7.1	2	33.3	12	63.2
Dehydration	none	4	50.0	9	64.3	3	50.0	3	15.8
	1-5%	4	50.0	4	28.6	2	33.3	9	47.4
	≥ 6%	0	0.0	1	7.1	1	16.7	7	36.8

Notes: N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 31: Percentage of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period, by mixed infection (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

	HRV $10^{4.7}$ N'= 22		HRV $10^{5.2}$ N'= 22		HRV $10^{5.8}$ N'= 15		Placebo N'= 55	
Mixed infection	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
At least one mixed infection	1	4.5	0	0.0	2	13.3	3	5.5
Campylobacter	0	0.0	0	0.0	0	0.0	0	0.0
Salmonella	1	4.5	0	0.0	0	0.0	0	0.0
Shigella	0	0.0	0	0.0	1	6.7	1	1.8
Ag-E.Coli	0	0.0	0	0.0	0	0.0	0	0.0
ETEC	0	0.0	0	0.0	0	0.0	0	0.0
EPEC	0	0.0	0	0.0	0	0.0	1	1.8
EAgEC	0	0.0	0	0.0	1	6.7	1	1.8
EIEC	0	0.0	0	0.0	0	0.0	0	0.0

Notes: N'= number of RV GE episodes reported
n/% = number/percentage of mixed RV GE episodes reported in each group, among all RV GE episodes reported in the first efficacy follow-up period

Supplement 32: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**p-value**
HRV $10^{4.7}$	507	22	300.2	0.073	0.048	0.111	4.3	2.7	6.5	59.2	32.0	76.3	<0.001
HRV $10^{5.2}$	508	22	297.7	0.074	0.049	0.112	4.3	2.7	6.5	59.3	32.1	76.4	<0.001
HRV $10^{5.8}$	512	15	301.7	0.050	0.030	0.082	2.9	1.6	4.8	72.5	50.6	85.6	<0.001
Pooled HRV Groups	1527	59	899.7	0.066	0.051	0.085	3.9	3.0	5.0	63.7	46.6	75.3	<0.001
Placebo	517	55	292.8	0.188	0.144	0.245	10.6	8.1	13.6	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode in the first efficacy follow-up period, in each group
% = Percentage of subjects reporting at least one RV GE episode in each group
n/T = person-year rate of RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 33: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
Brazil													
HRV $10^{4.7}$	186	16	116.2	0.138	0.084	0.225	8.6	5.0	13.6	41.6	-11.7	70.5	0.077
HRV $10^{5.2}$	182	18	111.9	0.161	0.101	0.255	9.9	6.0	15.2	32.9	-25.7	65.0	0.161
HRV $10^{5.8}$	192	10	121.3	0.082	0.044	0.153	5.2	2.5	9.4	64.7	25.0	84.7	0.002
Pooled HRV Groups	560	44	349.5	0.126	0.094	0.169	7.9	5.8	10.4	46.7	11.1	67.5	0.010
Placebo	190	28	114.0	0.246	0.170	0.356	14.7	10.0	20.6	-	-	-	-
Mexico													
HRV $10^{4.7}$	88	1	52.1	0.019	0.003	0.136	1.1	0.0	6.2	92.1	48.3	99.8	<0.001
HRV $10^{5.2}$	95	3	54.0	0.056	0.018	0.172	3.2	0.7	9.0	78.1	21.6	96.0	0.009
HRV $10^{5.8}$	90	3	50.9	0.059	0.019	0.183	3.3	0.7	9.4	76.9	17.3	95.7	0.010
Pooled HRV Groups	273	7	157.0	0.045	0.021	0.094	2.6	1.0	5.2	82.2	53.0	93.9	<0.001
Placebo	97	14	51.4	0.272	0.161	0.460	14.4	8.1	23.0	-	-	-	-
Venezuela													
HRV $10^{4.7}$	233	5	131.9	0.038	0.016	0.091	2.1	0.7	4.9	62.0	-13.5	89.4	0.057
HRV $10^{5.2}$	231	1	131.8	0.008	0.001	0.054	0.4	0.0	2.4	92.3	49.0	99.8	<0.001
HRV $10^{5.8}$	230	2	129.5	0.015	0.004	0.062	0.9	0.1	3.1	84.6	32.0	98.3	0.007
Pooled HRV Groups	694	8	393.2	0.020	0.010	0.041	1.2	0.5	2.3	79.6	46.9	92.7	<0.001
Placebo	230	13	127.4	0.102	0.059	0.176	5.7	3.0	9.5	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one RV GE episode in each group
n/T = person-year rate of RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 34: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
G1 wild type													
HRV $10^{4.7}$	507	13	302.9	0.043	0.025	0.074	2.6	1.4	4.3	57.2	15.9	79.5	0.008
HRV $10^{5.2}$	508	6	304.0	0.020	0.009	0.044	1.2	0.4	2.6	80.3	52.1	93.3	<0.001
HRV $10^{5.8}$	512	7	304.8	0.023	0.011	0.048	1.4	0.6	2.8	77.2	47.2	91.5	<0.001
Pooled HRV Groups	1527	26	911.8	0.029	0.019	0.042	1.7	1.1	2.5	71.6	50.6	83.8	<0.001
Placebo	517	31	301.1	0.103	0.072	0.146	6.0	4.1	8.4	-	-	-	-
G9													
HRV $10^{4.7}$	507	8	304.2	0.026	0.013	0.053	1.6	0.7	3.1	57.1	-2.7	83.7	0.049
HRV $10^{5.2}$	508	14	300.3	0.047	0.028	0.079	2.8	1.5	4.6	25.0	-57.7	65.2	0.480
HRV $10^{5.8}$	512	7	304.9	0.023	0.011	0.048	1.4	0.6	2.8	62.8	7.6	86.8	0.027
Pooled HRV Groups	1527	29	909.3	0.032	0.022	0.046	1.9	1.3	2.7	48.3	2.5	72.0	0.028
Placebo	517	19	303.3	0.063	0.040	0.098	3.7	2.2	5.7	-	-	-	-
Pooled Non G1 (G2, G3, G4, G9)													
HRV $10^{4.7}$	507	9	304.1	0.030	0.015	0.057	1.8	0.8	3.3	61.8	14.8	84.4	0.012
HRV $10^{5.2}$	508	14	300.3	0.047	0.028	0.079	2.8	1.5	4.6	40.6	-19.5	71.6	0.136
HRV $10^{5.8}$	512	8	304.2	0.026	0.013	0.053	1.6	0.7	3.1	66.3	22.6	86.9	0.006
Pooled HRV Groups	1527	31	908.6	0.034	0.024	0.049	2.0	1.4	2.9	56.3	22.1	75.2	0.003
Placebo	517	24	302.4	0.079	0.053	0.118	4.6	3.0	6.8	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one RV GE episode in each group
n/T = person-year rate of RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 35: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV $10^{4.7}$	507	13	303.5	0.043	0.025	0.074	2.6	1.4	4.3	66.9	36.7	83.7	<0.001
HRV $10^{5.2}$	508	10	302.5	0.033	0.018	0.061	2.0	0.9	3.6	74.6	48.2	88.7	<0.001
HRV $10^{5.8}$	512	5	305.6	0.016	0.007	0.039	1.0	0.3	2.3	87.4	68.0	96.1	<0.001
Pooled HRV Groups	1527	28	911.5	0.031	0.021	0.044	1.8	1.2	2.6	76.3	60.6	85.9	<0.001
Placebo	517	40	298.0	0.134	0.098	0.183	7.7	5.6	10.4	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 36: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
Brazil													
HRV $10^{4.7}$	186	9	118.8	0.076	0.039	0.146	4.8	2.2	9.0	60.0	10.3	83.7	0.015
HRV $10^{5.2}$	182	9	115.6	0.078	0.040	0.150	4.9	2.3	9.2	59.1	8.4	83.4	0.016
HRV $10^{5.8}$	192	4	123.3	0.032	0.012	0.086	2.1	0.6	5.2	82.8	49.6	95.7	<0.001
Pooled HRV Groups	560	22	357.8	0.061	0.040	0.093	3.9	2.5	5.9	67.5	39.1	82.8	<0.001
Placebo	190	23	115.4	0.199	0.132	0.300	12.1	7.8	17.6	-	-	-	-
Mexico													
HRV $10^{4.7}$	88	1	52.1	0.019	0.003	0.136	1.1	0.0	6.2	87.8	11.6	99.7	0.020
HRV $10^{5.2}$	95	0	55.0	0.000	Und.	Und.	0.0	0.0	3.8	100.0	48.3	100.0	0.003
HRV $10^{5.8}$	90	0	52.4	0.000	Und.	Und.	0.0	0.0	4.0	100.0	45.4	100.0	0.003
Pooled HRV Groups	273	1	159.5	0.006	0.001	0.045	0.4	0.0	2.0	96.1	71.5	99.9	<0.001
Placebo	97	9	53.4	0.169	0.088	0.324	9.3	4.3	16.9	-	-	-	-
Venezuela													
HRV $10^{4.7}$	233	3	132.5	0.023	0.007	0.070	1.3	0.3	3.7	63.0	-54.2	93.7	0.139
HRV $10^{5.2}$	231	1	131.8	0.008	0.001	0.054	0.4	0.0	2.4	87.6	7.2	99.7	0.020
HRV $10^{5.8}$	230	1	129.9	0.008	0.001	0.055	0.4	0.0	2.4	87.5	6.8	99.7	0.037
Pooled HRV Groups	694	5	394.2	0.013	0.005	0.030	0.7	0.2	1.7	79.3	28.2	94.7	0.005
Placebo	230	8	129.2	0.062	0.031	0.124	3.5	1.5	6.7	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
und = cannot be estimated
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 37: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
G1 wild type													
HRV $10^{4.7}$	507	8	304.5	0.026	0.013	0.053	1.6	0.7	3.1	54.7	-9.5	82.9	0.072
HRV $10^{5.2}$	508	4	304.7	0.013	0.005	0.035	0.8	0.2	2.0	77.4	31.3	94.4	0.004
HRV $10^{5.8}$	512	2	306.4	0.007	0.002	0.026	0.4	0.0	1.4	88.8	53.1	98.7	<0.001
Pooled HRV Groups	1527	14	915.6	0.015	0.009	0.026	0.9	0.5	1.5	73.7	44.0	87.9	<0.001
Placebo	517	18	305.4	0.059	0.037	0.094	3.5	2.1	5.4	-	-	-	-
G9													
HRV $10^{4.7}$	507	4	305.8	0.013	0.005	0.035	0.8	0.2	2.0	76.0	26.4	94.1	0.007
HRV $10^{5.2}$	508	6	303.6	0.020	0.009	0.044	1.2	0.4	2.6	64.1	4.5	88.4	0.033
HRV $10^{5.8}$	512	3	306.5	0.010	0.003	0.030	0.6	0.1	1.7	82.2	38.4	96.7	0.002
Pooled HRV Groups	1527	13	915.9	0.014	0.008	0.024	0.9	0.5	1.5	74.1	43.4	88.4	<0.001
Placebo	517	17	304.4	0.056	0.035	0.090	3.3	1.9	5.2	-	-	-	-
Pooled Non G1 (G2, G3, G4, G9)													
HRV $10^{4.7}$	507	5	305.8	0.016	0.007	0.039	1.0	0.3	2.3	75.7	33.8	92.8	0.002
HRV $10^{5.2}$	508	6	303.6	0.020	0.009	0.044	1.2	0.4	2.6	70.9	25.5	90.4	0.005
HRV $10^{5.8}$	512	3	306.5	0.010	0.003	0.030	0.6	0.1	1.7	85.6	51.7	97.2	<0.001
Pooled HRV Groups	1527	14	915.9	0.015	0.009	0.026	0.9	0.5	1.5	77.4	53.5	89.4	<0.001
Placebo	517	21	303.5	0.069	0.045	0.106	4.1	2.5	6.1	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 38: Percentage of subjects hospitalized due to RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV $10^{4.7}$	507	5	305.6	0.016	0.007	0.039	1.0	0.3	2.3	68.1	9.0	90.9	0.025
HRV $10^{5.2}$	508	1	305.5	0.003	0.000	0.023	0.2	0.0	1.1	93.6	59.1	99.8	<0.001
HRV $10^{5.8}$	512	3	306.3	0.010	0.003	0.030	0.6	0.1	1.7	81.1	33.9	96.5	0.004
Pooled HRV Groups	1527	9	917.4	0.010	0.005	0.019	0.6	0.3	1.1	81.0	54.2	92.6	<0.001
Placebo	517	16	305.3	0.052	0.032	0.086	3.1	1.8	5.0	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects hospitalized due to RV GE in each group
T = sum of follow-up period expressed in year censored at the first occurrence of hospitalization due to RV GE episode in the first efficacy follow-up period, in each group
n/N = percentage of subjects hospitalized due to RV GE in each group
n/T = person-year rate of hospitalization due to RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 39: Percentage of vaccinees reporting RV GE episodes from 2 weeks after Dose 2 up to the end of the first efficacy period, by status of anti-rotavirus IgA antibody concentration at two months after Dose 2 (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Anti-rotavirus	HRV $10^{4.7}$					HRV $10^{5.2}$				
Antibody status				95%CI					95%CI	
At Visit 3	N	n	%	LL	UL	N	n	%	LL	UL
Negative	70	8	11.4	5.1	21.3	58	6	10.3	3.9	21.2
Positive	110	1	0.9	0.0	5.0	107	2	1.9	0.2	6.6
Unknown	327	13	4.0	2.1	6.7	343	14	4.1	2.2	6.8

Anti-rotavirus	HRV $10^{5.8}$					Pooled HRV groups				
Antibody status				95%CI					95%CI	
At Visit 3	N	n	%	LL	UL	N	n	%	LL	UL
Negative	55	6	10.9	4.1	22.3	183	20	10.9	6.8	16.4
Positive	118	2	1.7	0.2	6.0	335	5	1.5	0.5	3.4
Unknown	339	7	2.1	0.8	4.2	1009	34	3.4	2.3	4.7

Notes: N = number of subjects included in the vaccine group with the specified status for anti-rotavirus IgA antibody concentration two months after Dose 2
n/%= number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration two months after Dose 2 reporting at least one RV GE episode from 2 weeks after Dose 2 up to the end of the first efficacy period
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 40: Percentage of subjects who reported any or severe RV GE episode(s) from day of Dose 1 till Day 14 after Dose 2 (total vaccinated cohort for subset planned to receive two doses of study vaccine)

Group	N	n	%	95%CI LL	UL
Any RV GE					
HRV $10^{4.7}$	538	14	2.6	1.4	4.3
HRV $10^{5.2}$	540	11	2.0	1.0	3.6
HRV $10^{5.8}$	540	11	2.0	1.0	3.6
Pooled HRV Groups	1618	36	2.2	1.6	3.1
Placebo	537	20	3.7	2.3	5.7
Severe RV GE					
HRV $10^{4.7}$	538	5	0.9	0.3	2.2
HRV $10^{5.2}$	540	4	0.7	0.2	1.9
HRV $10^{5.8}$	540	2	0.4	0.0	1.3
Pooled HRV Groups	1618	11	0.7	0.3	1.2
Placebo	537	10	1.9	0.9	3.4

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of specified intensity in each group
% = percentage of subjects reporting at least one RV GE episode of specified intensity in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 41: Percentage of subjects who reported any or severe RV GE episode(s) other than vaccine strain and efficacy of the vaccine from day of Dose 1 till Day 14 after Dose 2 (total vaccinated cohort for subset planned to receive two doses of study vaccine)

		n/N				Vaccine Efficacy		
				95%CI			95%CI	
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**
Any RV GE								
HRV $10^{4.7}$	538	10	1.9	0.9	3.4	50.1	-11.7	79.1
HRV $10^{5.2}$	540	6	1.1	0.4	2.4	70.2	23.0	90.2
HRV $10^{5.8}$	540	6	1.1	0.4	2.4	70.2	23.0	90.2
Pooled HRV Groups	1618	22	1.4	0.9	2.1	63.5	29.5	81.0
Placebo	537	20	3.7	2.3	5.7	-	-	-
Severe RV GE								
HRV $10^{4.7}$	538	5	0.9	0.3	2.2	50.1	-60.3	86.6
HRV $10^{5.2}$	540	2	0.4	0.0	1.3	80.1	6.7	97.9
HRV $10^{5.8}$	540	1	0.2	0.0	1.0	90.1	30.1	99.8
Pooled HRV Groups	1618	8	0.5	0.2	1.0	73.4	25.3	90.9
Placebo	537	10	1.9	0.9	3.4	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode other than vaccine strain of specified intensity in each group
% = percentage of subjects reporting at least one RV GE episode other than vaccine strain of specified intensity in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 42: Percentage of subjects who reported any or severe RV GE episode(s) and efficacy of the vaccine from day of Dose 1 till the end of the first efficacy follow-up period (total vaccinated cohort for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
Any RV GE													
HRV $10^{4.7}$	538	32	410.6	0.078	0.055	0.110	5.9	4.1	8.3	57.4	34.8	72.8	<0.001
HRV $10^{5.2}$	540	28	412.6	0.068	0.047	0.098	5.2	3.5	7.4	62.9	42.0	76.8	<0.001
HRV $10^{5.8}$	540	21	417.7	0.050	0.033	0.077	3.9	2.4	5.9	72.2	54.3	83.7	<0.001
Pooled HRV Groups	1618	81	1240.9	0.065	0.052	0.081	5.0	4.0	6.2	64.2	50.3	74.1	<0.001
Placebo	537	75	399.7	0.188	0.147	0.233	14.0	11.1	17.2	-	-	-	-
Severe RV GE													
HRV $10^{4.7}$	538	18	417.8	0.043	0.027	0.068	3.3	2.0	5.2	64.1	37.3	80.3	<0.001
HRV $10^{5.2}$	540	12	420.1	0.029	0.016	0.050	2.2	1.2	3.8	76.1	54.5	88.4	<0.001
HRV $10^{5.8}$	540	6	425.3	0.014	0.006	0.031	1.1	0.4	2.4	88.1	72.2	95.8	<0.001
Pooled HRV Groups	1618	36	1263.1	0.029	0.021	0.040	2.2	1.6	3.1	76.1	62.6	84.9	<0.001
Placebo	537	50	412.3	0.121	0.092	0.160	9.3	7.0	12.1	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of specified intensity in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of specified intensity in each group
% = percentage of subjects reporting at least one RV GE episode of specified intensity in each group
n/T = person-year rate of RV GE of specified intensity in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 43: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	538	114	21.2	17.8	24.9
	HRV_5.2	540	128	23.7	20.2	27.5
	HRV_5.8	540	140	25.9	22.3	29.8
	Pooled HRV groups	1618	382	23.6	21.6	25.8
	Placebo	537	129	24.0	20.5	27.9
Dose 2	**HRV_4.7**	510	105	20.6	17.2	24.4
	HRV_5.2	509	111	21.8	18.3	25.7
	HRV_5.8	515	114	22.1	18.6	26.0
	Pooled HRV groups	1534	330	21.5	19.5	23.7
	Placebo	522	104	19.9	16.6	23.6
Overall/dose	**HRV_4.7**	1048	219	20.9	18.5	23.5
	HRV_5.2	1049	239	22.8	20.3	25.4
	HRV_5.8	1055	254	24.1	21.5	26.8
	Pooled HRV groups	3152	712	22.6	21.1	24.1
	Placebo	1059	233	22.0	19.5	24.6
Overall/subject	**HRV_4.7**	538	180	33.5	29.5	37.6
	HRV_5.2	540	204	37.8	33.7	42.0
	HRV_5.8	540	196	36.3	32.2	40.5
	Pooled HRV groups	1618	580	35.8	33.5	38.2
	Placebo	537	190	35.4	31.3	39.6

Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N = number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom

Supplement 44: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15- day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	538	275	51.1	46.8	55.4
	HRV_5.2	540	278	51.5	47.2	55.8
	HRV_5.8	540	271	50.2	45.9	54.5
	Pooled HRV groups	1618	824	50.9	48.5	53.4
	Placebo	537	276	51.4	47.1	55.7
Dose 2	**HRV_4.7**	510	218	42.7	38.4	47.2
	HRV_5.2	509	234	46.0	41.6	50.4
	HRV_5.8	515	240	46.6	42.2	51.0
	Pooled HRV groups	1534	692	45.1	42.6	47.6
	Placebo	522	223	42.7	38.4	47.1
Overall/dose	**HRV_4.7**	1048	493	47.0	44.0	50.1
	HRV_5.2	1049	512	48.8	45.7	51.9
	HRV_5.8	1055	511	48.4	45.4	51.5
	Pooled HRV groups	3152	1516	48.1	46.3	49.9
	Placebo	1059	499	47.1	44.1	50.2
Overall/subject	**HRV_4.7**	538	285	53.0	48.7	57.3
	HRV_5.2	540	289	53.5	49.2	57.8
	HRV_5.8	540	287	53.1	48.8	57.4
	Pooled HRV groups	1618	861	53.2	50.7	55.7
	Placebo	537	281	52.3	48.0	56.6

Notes: exact 95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N = number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom

Supplement 45: Percentage of doses and subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/Dose											
Group		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		1048				1049				1055			
COUGH	Total	635	60.6	57.6	63.6	639	60.9	57.9	63.9	656	62.2	59.2	65.1
	Grade 2*3	335	32.0	29.1	34.9	313	29.8	27.1	32.7	343	32.5	29.7	35.4
	Grade 3	96	9.2	7.5	11.1	102	9.7	8.0	11.7	109	10.3	8.6	12.3
	Related	206	19.7	17.3	22.2	212	20.2	17.8	22.8	200	19.0	16.6	21.5
DIARRHEA	Total	71	6.8	5.3	8.5	68	6.5	5.1	8.1	88	8.3	6.7	10.2
	Grade 2*3	48	4.6	3.4	6.0	47	4.5	3.3	5.9	57	5.4	4.1	6.9
	Grade 3	16	1.5	0.9	2.5	23	2.2	1.4	3.3	24	2.3	1.5	3.4
	Related	35	3.3	2.3	4.6	43	4.1	3.0	5.5	50	4.7	3.5	6.2
IRRITABILITY	Total	673	64.2	61.2	67.1	683	65.1	62.1	68.0	704	66.7	63.8	69.6
	Grade 2*3	414	39.5	36.5	42.5	407	38.8	35.8	41.8	450	42.7	39.6	45.7
	Grade 3	118	11.3	9.4	13.3	112	10.7	8.9	12.7	124	11.8	9.9	13.9
	Related	404	38.5	35.6	41.6	400	38.1	35.2	41.1	418	39.6	36.7	42.6
LOSS OF APPETITE	Total	319	30.4	27.7	33.3	322	30.7	27.9	33.6	323	30.6	27.8	33.5
	Grade 2*3	117	11.2	9.3	13.2	112	10.7	8.9	12.7	131	12.4	10.5	14.6
	Grade 3	20	1.9	1.2	2.9	23	2.2	1.4	3.3	15	1.4	0.8	2.3
	Related	133	12.7	10.7	14.9	132	12.6	10.6	14.7	131	12.4	10.5	14.6
FEVER	Total	606	57.8	54.8	60.8	611	58.2	55.2	61.3	611	57.9	54.9	60.9
	Grade 2*3	233	22.2	19.7	24.9	226	21.5	19.1	24.2	240	22.7	20.3	25.4
	Grade 3	15	1.4	0.8	2.3	20	1.9	1.2	2.9	22	2.1	1.3	3.1
	Related	344	32.8	30.0	35.8	316	30.1	27.4	33.0	332	31.5	28.7	34.4
VOMITING	Total	143	13.6	11.6	15.9	175	16.7	14.5	19.1	156	14.8	12.7	17.1
	Grade 2*3	62	5.9	4.6	7.5	102	9.7	8.0	11.7	80	7.6	6.1	9.3
	Grade 3	25	2.4	1.5	3.5	46	4.4	3.2	5.8	42	4.0	2.9	5.3
	Related	80	7.6	6.1	9.4	79	7.5	6.0	9.3	63	6.0	4.6	7.6

Notes: exact 95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination

Supplement 45(continued): Percentage of doses and subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/Dose							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		3152				1059			
COUGH	Total	1930	61.2	59.5	62.9	671	63.4	60.4	66.3
	Grade 2*3	991	31.4	29.8	33.1	372	35.1	32.2	38.1
	Grade 3	307	9.7	8.7	10.8	80	7.6	6.0	9.3
	Related	618	19.6	18.2	21.0	208	19.6	17.3	22.2
DIARRHEA	Total	227	7.2	6.3	8.2	91	8.6	7.0	10.4
	Grade 2*3	152	4.8	4.1	5.6	60	5.7	4.4	7.2
	Grade 3	63	2.0	1.5	2.6	25	2.4	1.5	3.5
	Related	128	4.1	3.4	4.8	43	4.1	3.0	5.4
IRRITABILITY	Total	2060	65.4	63.7	67.0	713	67.3	64.4	70.1
	Grade 2*3	1271	40.3	38.6	42.1	449	42.4	39.4	45.4
	Grade 3	354	11.2	10.1	12.4	124	11.7	9.8	13.8
	Related	1222	38.8	37.1	40.5	407	38.4	35.5	41.4
LOSS OF APPETITE	Total	964	30.6	29.0	32.2	336	31.7	28.9	34.6
	Grade 2*3	360	11.4	10.3	12.6	134	12.7	10.7	14.8
	Grade 3	58	1.8	1.4	2.4	20	1.9	1.2	2.9
	Related	396	12.6	11.4	13.8	145	13.7	11.7	15.9
FEVER	Total	1828	58.0	56.2	59.7	634	59.9	56.8	62.8
	Grade 2*3	699	22.2	20.7	23.7	222	21.0	18.5	23.5
	Grade 3	57	1.8	1.4	2.3	22	2.1	1.3	3.1
	Related	992	31.5	29.9	33.1	317	29.9	27.2	32.8
VOMITING	Total	474	15.0	13.8	16.3	148	14.0	11.9	16.2
	Grade 2*3	244	7.7	6.8	8.7	73	6.9	5.4	8.6
	Grade 3	113	3.6	3.0	4.3	28	2.6	1.8	3.8
	Related	222	7.0	6.2	8.0	78	7.4	5.9	9.1

Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination

Supplement 45(continued): Percentage of doses and subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/Subject											
Group		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		538				540				540			
COUGH	Total	420	78.1	74.3	81.5	420	77.8	74.0	81.2	423	78.3	74.6	81.7
	Grade 2*3	247	45.9	41.6	50.2	249	46.1	41.8	50.4	258	47.8	43.5	52.1
	Grade 3	88	16.4	13.3	19.8	91	16.9	13.8	20.3	92	17.0	14.0	20.5
	Related	157	29.2	25.4	33.2	168	31.1	27.2	35.2	164	30.4	26.5	34.4
DIARRHEA	Total	68	12.6	10.0	15.7	61	11.3	8.8	14.3	77	14.3	11.4	17.5
	Grade 2*3	46	8.6	6.3	11.2	45	8.3	6.1	11.0	52	9.6	7.3	12.4
	Grade 3	16	3.0	1.7	4.8	23	4.3	2.7	6.3	23	4.3	2.7	6.3
	Related	35	6.5	4.6	8.9	41	7.6	5.5	10.2	45	8.3	6.1	11.0
IRRITABILITY	Total	422	78.4	74.7	81.8	436	80.7	77.2	84.0	441	81.7	78.1	84.8
	Grade 2*3	305	56.7	52.4	60.9	305	56.5	52.2	60.7	318	58.9	54.6	63.1
	Grade 3	97	18.0	14.9	21.5	97	18.0	14.8	21.5	95	17.6	14.5	21.1
	Related	254	47.2	42.9	51.5	252	46.7	42.4	51.0	267	49.4	45.1	53.7
LOSS OF APPETITE	Total	240	44.6	40.4	48.9	246	45.6	41.3	49.9	241	44.6	40.4	48.9
	Grade 2*3	103	19.1	15.9	22.7	98	18.1	15.0	21.7	111	20.6	17.2	24.2
	Grade 3	18	3.3	2.0	5.2	21	3.9	2.4	5.9	15	2.8	1.6	4.5
	Related	109	20.3	16.9	23.9	108	20.0	16.7	23.6	104	19.3	16.0	22.8
FEVER	Total	410	76.2	72.4	79.7	422	78.1	74.4	81.6	406	75.2	71.3	78.8
	Grade 2*3	194	36.1	32.0	40.3	195	36.1	32.1	40.3	198	36.7	32.6	40.9
	Grade 3	15	2.8	1.6	4.6	20	3.7	2.3	5.7	21	3.9	2.4	5.9
	Related	236	43.9	39.6	48.2	223	41.3	37.1	45.6	224	41.5	37.3	45.8
VOMITING	Total	122	22.7	19.2	26.5	148	27.4	23.7	31.4	133	24.6	21.1	28.5
	Grade 2*3	54	10.0	7.6	12.9	91	16.9	13.8	20.3	74	13.7	10.9	16.9
	Grade 3	24	4.5	2.9	6.6	44	8.1	6.0	10.8	39	7.2	5.2	9.7
	Related	68	12.6	10.0	15.7	70	13.0	10.2	16.1	56	10.4	7.9	13.3

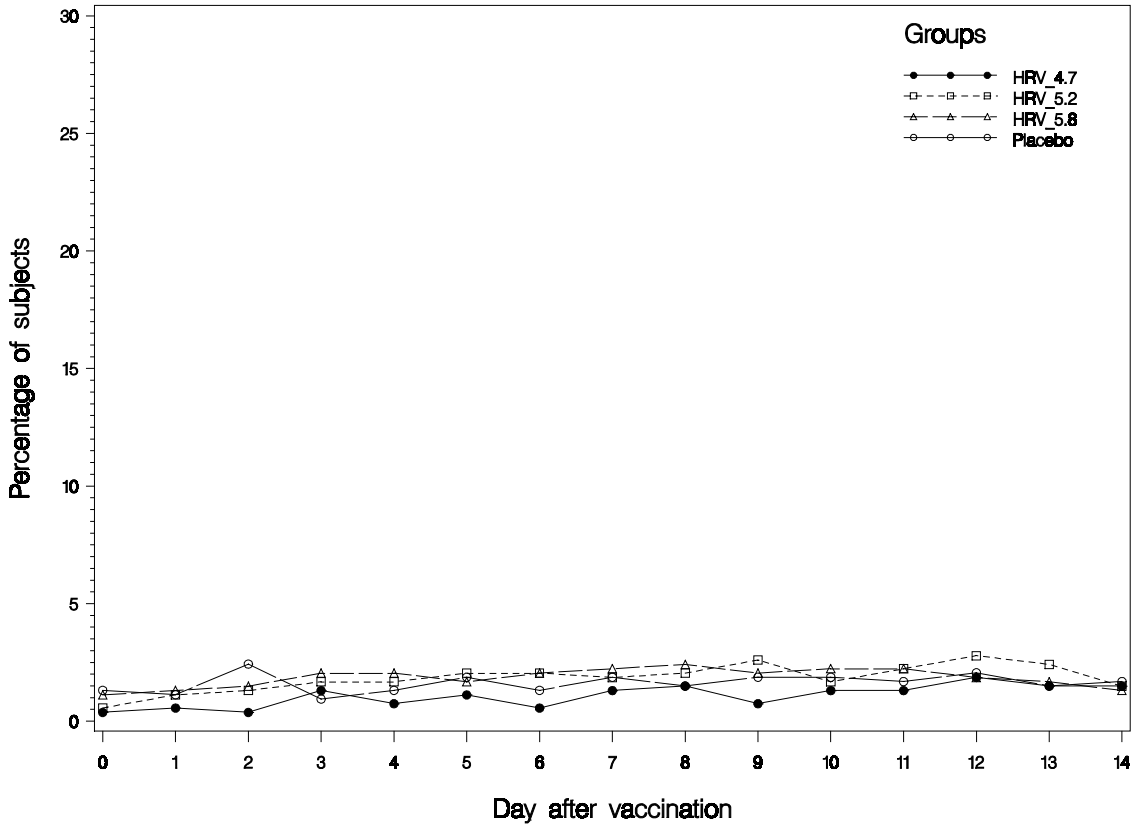
Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination

Supplement 45(continued): Percentage of doses and subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/subject							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		1618				537			
COUGH	Total	1263	78.1	76.0	80.1	437	81.4	77.8	84.6
	Grade 2*3	754	46.6	44.1	49.1	287	53.4	49.1	57.7
	Grade 3	271	16.7	15.0	18.7	71	13.2	10.5	16.4
	Related	489	30.2	28.0	32.5	162	30.2	26.3	34.2
DIARRHEA	Total	206	12.7	11.1	14.5	85	15.8	12.8	19.2
	Grade 2*3	143	8.8	7.5	10.3	58	10.8	8.3	13.7
	Grade 3	62	3.8	3.0	4.9	23	4.3	2.7	6.4
	Related	121	7.5	6.2	8.9	41	7.6	5.5	10.2
IRRITABILITY	Total	1299	80.3	78.3	82.2	444	82.7	79.2	85.8
	Grade 2*3	928	57.4	54.9	59.8	328	61.1	56.8	65.2
	Grade 3	289	17.9	16.0	19.8	109	20.3	17.0	24.0
	Related	773	47.8	45.3	50.2	258	48.0	43.7	52.4
LOSS OF APPETITE	Total	727	44.9	42.5	47.4	252	46.9	42.6	51.2
	Grade 2*3	312	19.3	17.4	21.3	113	21.0	17.7	24.7
	Grade 3	54	3.3	2.5	4.3	20	3.7	2.3	5.7
	Related	321	19.8	17.9	21.9	118	22.0	18.5	25.7
FEVER	Total	1238	76.5	74.4	78.6	425	79.1	75.5	82.5
	Grade 2*3	587	36.3	33.9	38.7	184	34.3	30.3	38.4
	Grade 3	56	3.5	2.6	4.5	21	3.9	2.4	5.9
	Related	683	42.2	39.8	44.7	224	41.7	37.5	46.0
VOMITING	Total	403	24.9	22.8	27.1	129	24.0	20.5	27.9
	Grade 2*3	219	13.5	11.9	15.3	67	12.5	9.8	15.6
	Grade 3	107	6.6	5.5	7.9	27	5.0	3.3	7.2
	Related	194	12.0	10.4	13.7	70	13.0	10.3	16.2

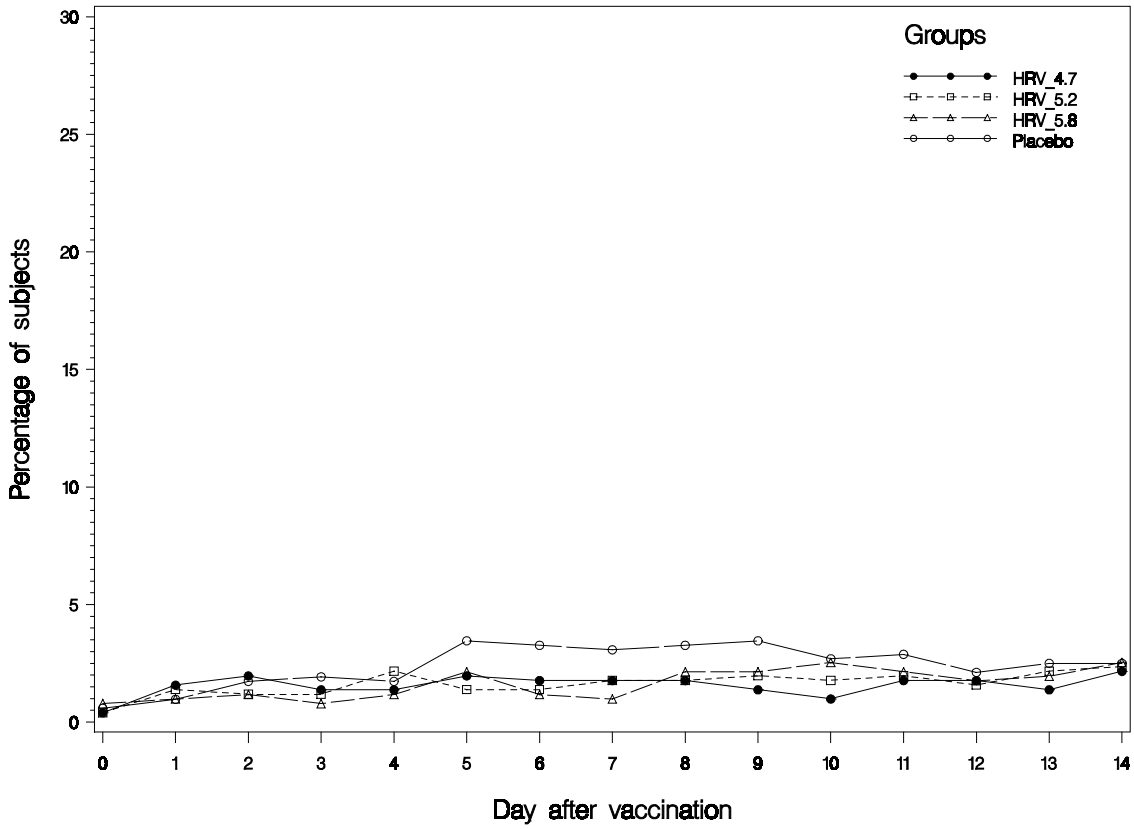
Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination

Supplement 46: Prevalence of diarrhea by day after vaccination, during the solicited 15-day follow-up period after Dose 1 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



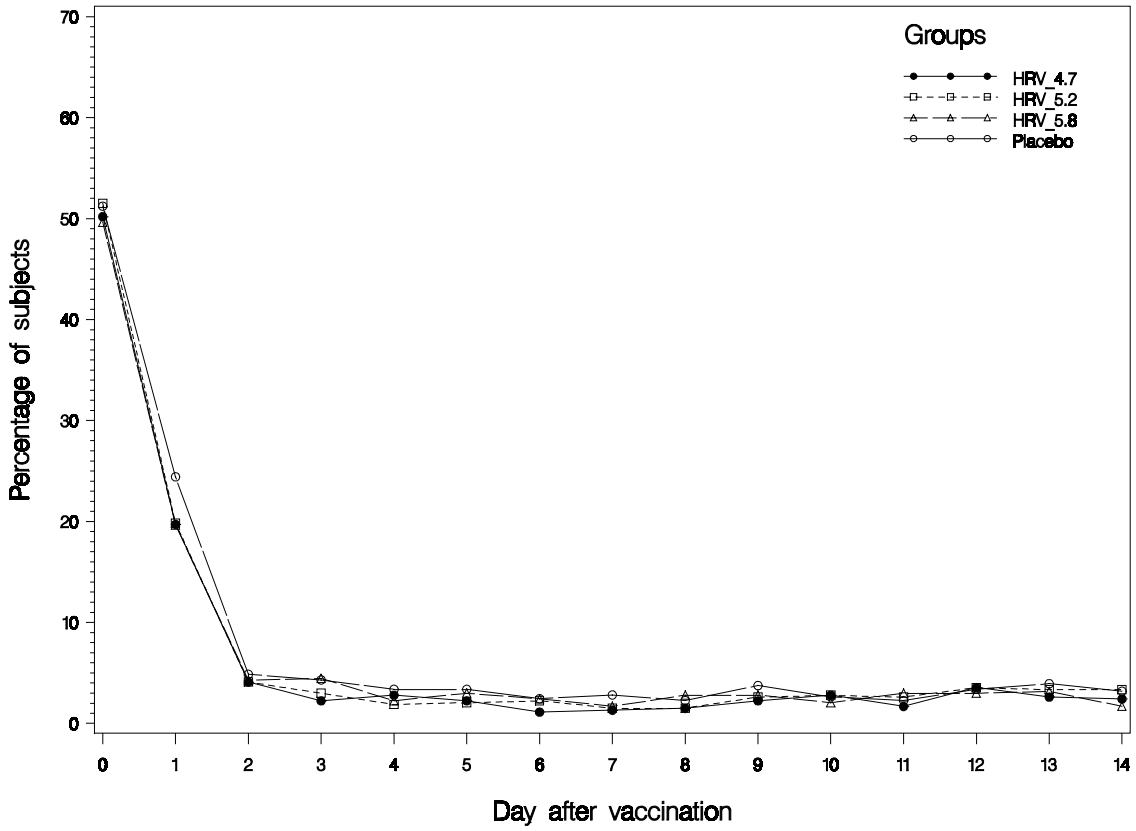
Notes: D0 = day of vaccination, D1 = on day after vaccination,…

Supplement 47: Prevalence of diarrhea by day after vaccination, during the solicited 15-day follow-up period after Dose 2 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



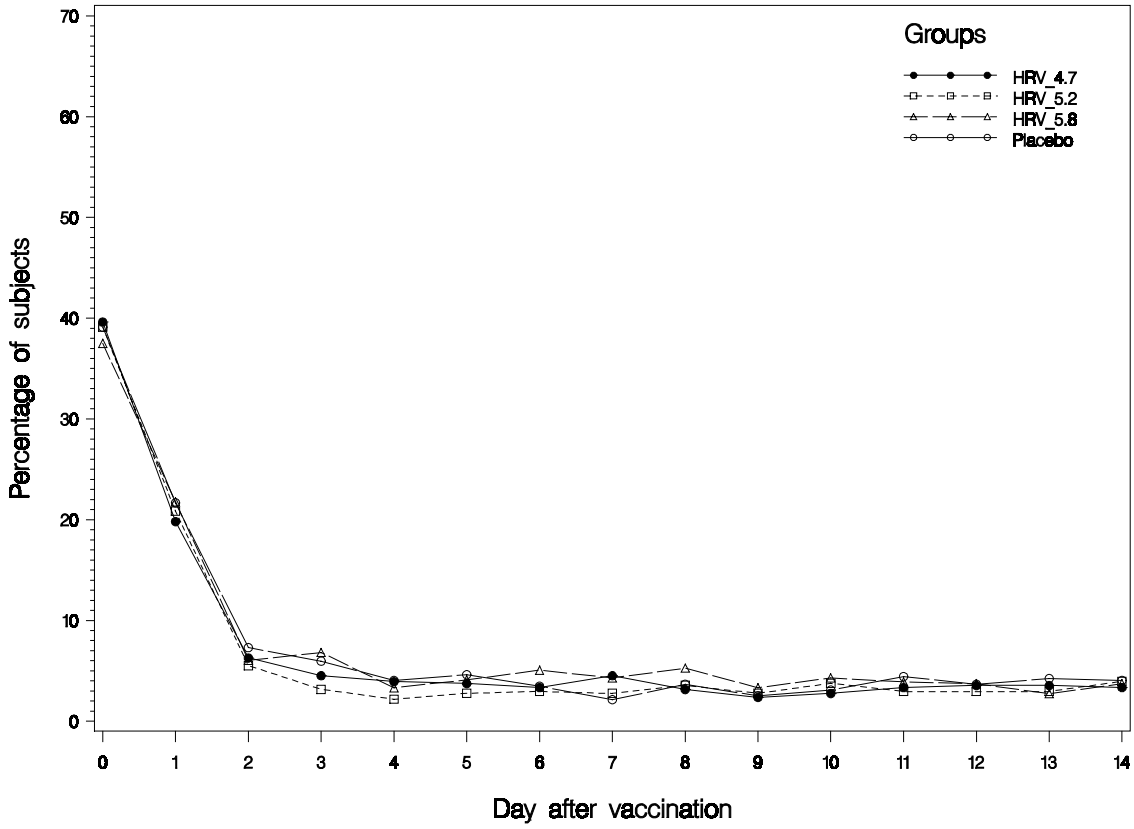
Notes: D0 = day of vaccination, D1 = on day after vaccination,…

Supplement 48: Prevalence of fever by day after vaccination, during the solicited 15-day follow-up period after Dose 1 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



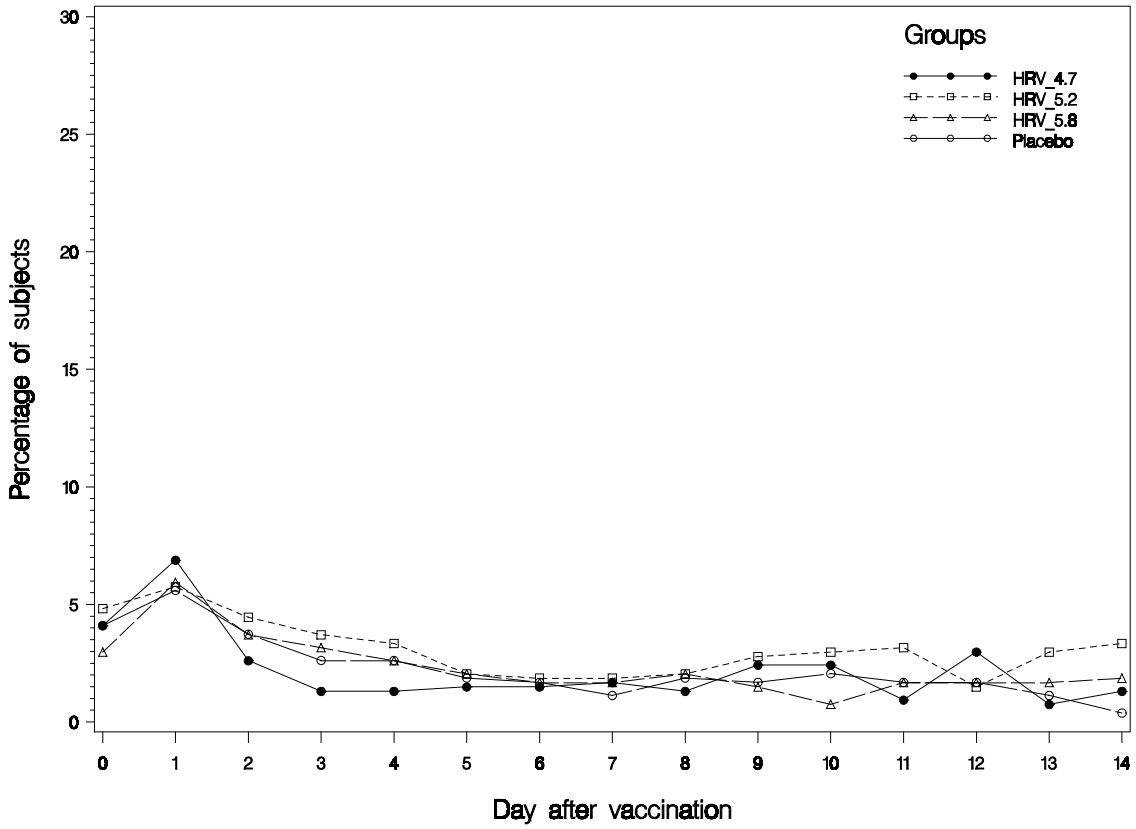
Notes: D0 = day of vaccination, D1 = on day after vaccination,…

Supplement 49: Prevalence of fever by day after vaccination, during the solicited 15-day follow-up period after Dose 2 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



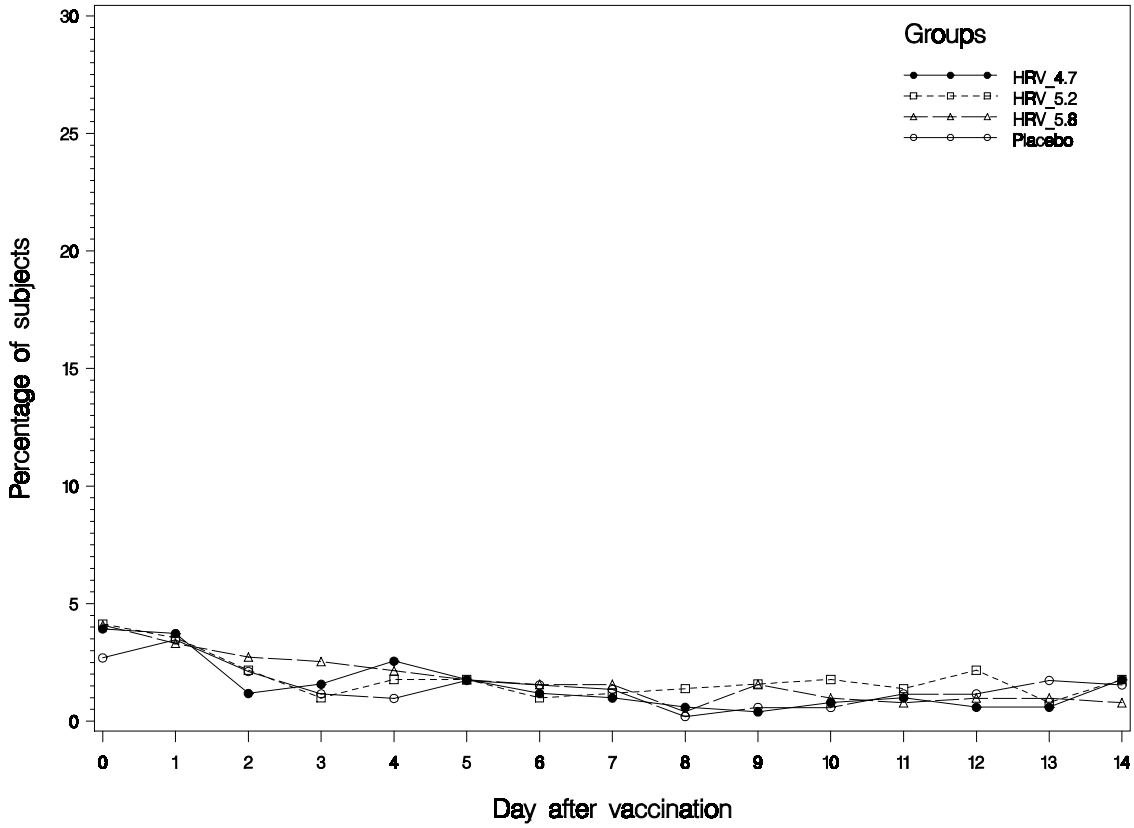
Notes: D0 = day of vaccination, D1 = on day after vaccination,…

Supplement 50: Prevalence of vomiting by day after vaccination, during the solicited 15-day follow-up period after Dose 1 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



Notes: D0 = day of vaccination, D1 = on day after vaccination

Supplement 51: Prevalence of vomiting by day after vaccination, during the solicited 15-day follow-up period after Dose 2 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



Notes: D0 = day of vaccination, D1 = on day after vaccination

Supplement 52: Duration (in days) of diarrhea, vomiting and fever during the solicited 15-day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Solicited symptom	Dose	Group	n	Mean	Min	Q1	Median	Q3	Max
Fever	Dose 1	HRV_4.7	331	1.6	1.0	1.0	1.0	2.0	8.0
		HRV_5.2	339	1.7	1.0	1.0	1.0	2.0	12.0
		HRV_5.8	331	1.7	1.0	1.0	1.0	2.0	8.0
		Pooled HRV groups	1001	1.7	1.0	1.0	1.0	2.0	12.0
		Placebo	346	1.8	1.0	1.0	1.0	2.0	15.0
	Dose 2	HRV_4.7	275	2.0	1.0	1.0	2.0	2.0	11.0
		HRV_5.2	272	1.9	1.0	1.0	1.0	2.0	12.0
		HRV_5.8	279	2.1	1.0	1.0	2.0	3.0	9.0
		Pooled HRV groups	826	2.0	1.0	1.0	2.0	2.0	12.0
		Placebo	288	2.1	1.0	1.0	2.0	2.0	9.0
	All/Dose	HRV_4.7	606	1.8	1.0	1.0	1.0	2.0	11.0
		HRV_5.2	611	1.8	1.0	1.0	1.0	2.0	12.0
		HRV_5.8	610	1.9	1.0	1.0	1.0	2.0	9.0
		Pooled HRV groups	1827	1.8	1.0	1.0	1.0	2.0	12.0
		Placebo	634	1.9	1.0	1.0	1.5	2.0	15.0
Vomiting	Dose 1	HRV_4.7	88	2.0	1.0	1.0	1.0	2.0	14.0
		HRV_5.2	106	2.4	1.0	1.0	1.0	3.0	12.0
		HRV_5.8	90	2.1	1.0	1.0	2.0	3.0	6.0
		Pooled HRV groups	284	2.2	1.0	1.0	1.0	2.0	14.0
		Placebo	89	2.0	1.0	1.0	1.0	2.0	11.0
	Dose 2	HRV_4.7	55	2.1	1.0	1.0	1.0	3.0	8.0
		HRV_5.2	69	2.0	1.0	1.0	1.0	3.0	6.0
		HRV_5.8	65	2.1	1.0	1.0	1.0	3.0	8.0
		Pooled HRV groups	189	2.1	1.0	1.0	1.0	3.0	8.0
		Placebo	59	1.9	1.0	1.0	1.0	2.0	7.0
	All/Dose	HRV_4.7	143	2.0	1.0	1.0	1.0	2.0	14.0
		HRV_5.2	175	2.2	1.0	1.0	1.0	3.0	12.0
		HRV_5.8	155	2.1	1.0	1.0	2.0	3.0	8.0
		Pooled HRV groups	473	2.1	1.0	1.0	1.0	3.0	14.0
		Placebo	148	2.0	1.0	1.0	1.0	2.0	11.0
Diarrhea	Dose 1	HRV_4.7	33	2.6	1.0	1.0	2.0	3.0	9.0
		HRV_5.2	34	4.4	1.0	2.0	3.0	6.0	14.0
		HRV_5.8	44	3.4	1.0	1.0	2.0	5.0	11.0
		Pooled HRV groups	111	3.5	1.0	1.0	2.0	5.0	14.0
		Placebo	45	2.9	1.0	1.0	2.0	4.0	12.0
	Dose 2	HRV_4.7	38	3.1	1.0	1.0	2.0	5.0	12.0
		HRV_5.2	34	3.6	1.0	1.0	3.0	5.0	13.0
		HRV_5.8	44	2.8	1.0	1.0	2.0	4.0	11.0
		Pooled HRV groups	116	3.2	1.0	1.0	2.0	5.0	13.0
		Placebo	46	4.1	1.0	1.0	3.5	6.0	13.0
	All/Dose	HRV_4.7	71	2.9	1.0	1.0	2.0	4.0	12.0
		HRV_5.2	68	4.0	1.0	1.0	3.0	6.0	14.0
		HRV_5.8	88	3.1	1.0	1.0	2.0	5.0	11.0
		Pooled HRV groups	227	3.3	1.0	1.0	2.0	5.0	14.0
		Placebo	91	3.5	1.0	1.0	3.0	5.0	13.0

Notes: n = number of doses reporting the specified solicited symptom
Q1 = 25th percentile
Q3 = 75th percentile

Supplement 53: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 538				HRV_5.2 N = 540				HRV_5.8 N = 540				Pooled HRV groups N = 1618				Placebo N = 537			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		350	65.1	60.9	69.1	354	65.6	61.4	69.6	328	60.7	56.5	64.9	1032	63.8	61.4	66.1	342	63.7	59.5	67.8
Application site (1820)	Dermatitis contact (0049)	4	0.7	0.2	1.9	8	1.5	0.6	2.9	4	0.7	0.2	1.9	16	1	0.6	1.6	6	1.1	0.4	2.4
	Injection site reaction (0058)	7	1.3	0.5	2.7	5	0.9	0.3	2.1	5	0.9	0.3	2.1	17	1.1	0.6	1.7	7	1.3	0.5	2.7
	Otitis externa (0059)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1	1	0.1	0	0.3	0	0	0	0.7
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.7	2	0.4	0	1.3	1	0.2	0	1	3	0.2	0	0.5	1	0.2	0	1
	Allergic reaction (0712)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	3	0.6	0.1	1.6
	Allergy (1058)	3	0.6	0.1	1.6	12	2.2	1.2	3.8	6	1.1	0.4	2.4	21	1.3	0.8	2	9	1.7	0.8	3.2
	Death, nos (0722)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1	1	0.1	0	0.3	0	0	0	0.7
	Edema generalised (0400)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
	Fever (0725)	44	8.2	6	10.8	44	8.1	6	10.8	45	8.3	6.1	11	133	8.2	6.9	9.7	41	7.6	5.5	10.2
	Injury (9001)	5	0.9	0.3	2.2	0	0	0	0.7	0	0	0	0.7	5	0.3	0.1	0.7	0	0	0	0.7
	Pallor (0220)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
Cardiovascular general (1010)	Cyanosis (0501)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	0.7	2	0.4	0	1.3	0	0	0	0.7	2	0.1	0	0.4	1	0.2	0	1
	Fever convulsions (1357)	1	0.2	0	1	0	0	0	0.7	1	0.2	0	1	2	0.1	0	0.4	0	0	0	0.7
	Spasm generalized (0149)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
	Vascular malformation peripheral (0764)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 53 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 538				HRV_5.2 N = 540				HRV_5.8 N = 540				Pooled HRV groups N = 1618				Placebo N = 537			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Gastrointestinal system (600)	Abdominal pain (0268)	33	6.1	4.3	8.5	30	5.6	3.8	7.8	25	4.6	3	6.8	88	5.4	4.4	6.7	25	4.7	3	6.8
	Anorexia (0165)	21	3.9	2.4	5.9	21	3.9	2.4	5.9	14	2.6	1.4	4.3	56	3.5	2.6	4.5	26	4.8	3.2	7
	Anus disorder (0269)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
	Constipation (0204)	11	2	1	3.6	11	2	1	3.6	10	1.9	0.9	3.4	32	2	1.4	2.8	6	1.1	0.4	2.4
	Gastroenteritis (0293)	3	0.6	0.1	1.6	5	0.9	0.3	2.1	1	0.2	0	1	9	0.6	0.3	1.1	4	0.7	0.2	1.9
	Gastroesophageal reflux (1149)	4	0.7	0.2	1.9	7	1.3	0.5	2.7	7	1.3	0.5	2.7	18	1.1	0.7	1.8	3	0.6	0.1	1.6
	Gastrointestinal disorder nos (1262)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1	1	0.1	0	0.3	1	0.2	0	1
	Stomatitis (0327)	0	0	0	0.7	1	0.2	0	1	1	0.2	0	1	2	0.1	0	0.4	1	0.2	0	1
	Stomatitis aphthous (0751)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
	Vomiting (0228)	14	2.6	1.4	4.3	17	3.1	1.8	5	16	3	1.7	4.8	47	2.9	2.1	3.8	20	3.7	2.3	5.7
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
	Earache (0260)	2	0.4	0	1.3	1	0.2	0	1	1	0.2	0	1	4	0.2	0.1	0.6	2	0.4	0	1.3
Neoplasm (1700)	Neoplasm nos (1259)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
Psychiatric (500)	Nervousness (0188)	30	5.6	3.8	7.9	26	4.8	3.2	7	30	5.6	3.8	7.8	86	5.3	4.3	6.5	34	6.3	4.4	8.7
Red blood cell (1210)	Anemia (0544)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
Reproductive female (1420)	Leukorrhea (0654)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1	1	0.1	0	0.3	0	0	0	0.7
Resistance mechanism (1830)	Abscess (0887)	1	0.2	0	1	2	0.4	0	1.3	3	0.6	0.1	1.6	6	0.4	0.1	0.8	0	0	0	0.7
	Infection (0736)	26	4.8	3.2	7	22	4.1	2.6	6.1	18	3.3	2	5.2	66	4.1	3.2	5.2	24	4.5	2.9	6.6
	Infection bacterial (0738)	1	0.2	0	1	2	0.4	0	1.3	0	0	0	0.7	3	0.2	0	0.5	1	0.2	0	1

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 53 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 538				HRV_5.2 N = 540				HRV_5.8 N = 540				Pooled HRV groups N = 1618				Placebo N = 537			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
	Infection viral (0740)	171	31.8	27.9	35.9	160	29.6	25.8	33.7	155	28.7	24.9	32.7	486	30	27.8	32.3	171	31.8	27.9	36
	Moniliasis (0741)	7	1.3	0.5	2.7	12	2.2	1.2	3.8	3	0.6	0.1	1.6	22	1.4	0.9	2.1	5	0.9	0.3	2.2
	Otitis media (0750)	5	0.9	0.3	2.2	11	2	1	3.6	3	0.6	0.1	1.6	19	1.2	0.7	1.8	11	2	1	3.6
	Upper resp tract infection (0543)	41	7.6	5.5	10.2	36	6.7	4.7	9.1	44	8.1	6	10.8	121	7.5	6.2	8.9	40	7.4	5.4	10
Respiratory system (1100)	Asthma (1367)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
	Atelectasis (1197)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
	Bronchitis (0805)	21	3.9	2.4	5.9	30	5.6	3.8	7.8	21	3.9	2.4	5.9	72	4.4	3.5	5.6	14	2.6	1.4	4.3
	Bronchospasm (0511)	14	2.6	1.4	4.3	9	1.7	0.8	3.1	12	2.2	1.2	3.8	35	2.2	1.5	3	7	1.3	0.5	2.7
	Coughing (0513)	30	5.6	3.8	7.9	25	4.6	3	6.8	29	5.4	3.6	7.6	84	5.2	4.2	6.4	20	3.7	2.3	5.7
	Dyspnea (0514)	0	0	0	0.7	1	0.2	0	1	1	0.2	0	1	2	0.1	0	0.4	1	0.2	0	1
	Laryngitis (0521)	1	0.2	0	1	3	0.6	0.1	1.6	2	0.4	0	1.3	6	0.4	0.1	0.8	2	0.4	0	1.3
	Pharyngitis (0523)	59	11	8.5	13.9	74	13.7	10.9	16.9	64	11.9	9.2	14.9	197	12.2	10.6	13.9	70	13	10.3	16.2
	Pneumonia (0528)	14	2.6	1.4	4.3	25	4.6	3	6.8	20	3.7	2.3	5.7	59	3.6	2.8	4.7	20	3.7	2.3	5.7
	Respiratory disorder (0536)	0	0	0	0.7	6	1.1	0.4	2.4	1	0.2	0	1	7	0.4	0.2	0.9	2	0.4	0	1.3
	Rhinitis (0539)	9	1.7	0.8	3.2	15	2.8	1.6	4.5	12	2.2	1.2	3.8	36	2.2	1.6	3.1	14	2.6	1.4	4.3
	Sputum increased (0541)	3	0.6	0.1	1.6	8	1.5	0.6	2.9	2	0.4	0	1.3	13	0.8	0.4	1.4	3	0.6	0.1	1.6
Secondary term (2000)	Varicella (1516)	2	0.4	0	1.3	1	0.2	0	1	1	0.2	0	1	4	0.2	0.1	0.6	4	0.7	0.2	1.9
Skin and appendages (100)	Alopecia (0002)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
	Dermatitis (0007)	2	0.4	0	1.3	4	0.7	0.2	1.9	5	0.9	0.3	2.1	11	0.7	0.3	1.2	0	0	0	0.7
	Dermatitis fungal (0009)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
	Furunculosis (0016)	3	0.6	0.1	1.6	1	0.2	0	1	1	0.2	0	1	5	0.3	0.1	0.7	0	0	0	0.7

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 53 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 538				HRV_5.2 N = 540				HRV_5.8 N = 540				Pooled HRV groups N = 1618				Placebo N = 537			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
	Photosensitivity reaction (0022)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
	Pruritus (0024)	0	0	0	0.7	3	0.6	0.1	1.6	2	0.4	0	1.3	5	0.3	0.1	0.7	0	0	0	0.7
	Rash (0027)	1	0.2	0	1	1	0.2	0	1	0	0	0	0.7	2	0.1	0	0.4	0	0	0	0.7
	Rash erythematous (0028)	2	0.4	0	1.3	1	0.2	0	1	0	0	0	0.7	3	0.2	0	0.5	1	0.2	0	1
	Rash maculo-papular (0030)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7	1	0.1	0	0.3	1	0.2	0	1
	Rash pustular (0032)	0	0	0	0.7	2	0.4	0	1.3	3	0.6	0.1	1.6	5	0.3	0.1	0.7	2	0.4	0	1.3
	Seborrhea (0033)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
	Skin disorder (0037)	6	1.1	0.4	2.4	8	1.5	0.6	2.9	9	1.7	0.8	3.1	23	1.4	0.9	2.1	10	1.9	0.9	3.4
	Sweat gland disorder (1166)	1	0.2	0	1	1	0.2	0	1	2	0.4	0	1.3	4	0.2	0.1	0.6	0	0	0	0.7
Urinary system (1300)	Dysuria (0601)	0	0	0	0.7	1	0.2	0	1	2	0.4	0	1.3	3	0.2	0	0.5	0	0	0	0.7
	Urinary tract infection (0628)	0	0	0	0.7	0	0	0	0.7	2	0.4	0	1.3	2	0.1	0	0.4	2	0.4	0	1.3
Vision (431)	Blepharitis (1007)	1	0.2	0	1	0	0	0	0.7	1	0.2	0	1	2	0.1	0	0.4	0	0	0	0.7
	Conjunctivitis (0238)	13	2.4	1.3	4.1	13	2.4	1.3	4.1	9	1.7	0.8	3.1	35	2.2	1.5	3	10	1.9	0.9	3.4
White cell and reticuloendothelial system (1220)	Lymphadenopathy cervical (0578)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1	1	0.1	0	0.3	0	0	0	0.7

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 54: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		482	46	42.9	49.1	495	47.2	44.1	50.3	460	43.6	40.6	46.7	1437	45.6	43.8	47.3	475	44.9	41.8	47.9
Application site (1820)	Dermatitis contact (0049)	4	0.4	0.1	1	8	0.8	0.3	1.5	4	0.4	0.1	1	16	0.5	0.3	0.8	7	0.7	0.3	1.4
	Injection site reaction (0058)	7	0.7	0.3	1.4	5	0.5	0.2	1.1	5	0.5	0.2	1.1	17	0.5	0.3	0.9	8	0.8	0.3	1.5
	Otitis externa (0059)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	0	0	0	0.3
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.4	2	0.2	0	0.7	1	0.1	0	0.5	3	0.1	0	0.3	1	0.1	0	0.5
	Allergic reaction (0712)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	3	0.3	0.1	0.8
	Allergy (1058)	3	0.3	0.1	0.8	14	1.3	0.7	2.2	6	0.6	0.2	1.2	23	0.7	0.5	1.1	9	0.8	0.4	1.6
	Death, nos (0722)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	0	0	0	0.3
	Edema generalised (0400)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Fever (0725)	45	4.3	3.1	5.7	46	4.4	3.2	5.8	47	4.5	3.3	5.9	138	4.4	3.7	5.2	43	4.1	3	5.4
	Injury (9001)	5	0.5	0.2	1.1	0	0	0	0.4	0	0	0	0.3	5	0.2	0.1	0.4	0	0	0	0.3
	Pallor (0220)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Cardiovascular general (1010)	Cyanosis (0501)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	0.4	2	0.2	0	0.7	0	0	0	0.3	2	0.1	0	0.2	1	0.1	0	0.5
	Fever convulsions (1357)	1	0.1	0	0.5	0	0	0	0.4	1	0.1	0	0.5	2	0.1	0	0.2	0	0	0	0.3
	Spasm generalized (0149)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Vascular malformation peripheral (0764)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 54 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Gastrointestinal system (600)	Abdominal pain (0268)	35	3.3	2.3	4.6	31	3	2	4.2	30	2.8	1.9	4	96	3	2.5	3.7	25	2.4	1.5	3.5
	Anorexia (0165)	24	2.3	1.5	3.4	23	2.2	1.4	3.3	15	1.4	0.8	2.3	62	2	1.5	2.5	27	2.5	1.7	3.7
	Anus disorder (0269)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Constipation (0204)	11	1	0.5	1.9	12	1.1	0.6	2	11	1	0.5	1.9	34	1.1	0.7	1.5	6	0.6	0.2	1.2
	Gastroenteritis (0293)	3	0.3	0.1	0.8	5	0.5	0.2	1.1	1	0.1	0	0.5	9	0.3	0.1	0.5	4	0.4	0.1	1
	Gastroesophageal reflux (1149)	4	0.4	0.1	1	7	0.7	0.3	1.4	7	0.7	0.3	1.4	18	0.6	0.3	0.9	3	0.3	0.1	0.8
	Gastrointestinal disorder nos (1262)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	1	0.1	0	0.5
	Stomatitis (0327)	0	0	0	0.4	1	0.1	0	0.5	1	0.1	0	0.5	2	0.1	0	0.2	1	0.1	0	0.5
	Stomatitis aphthous (0751)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Vomiting (0228)	14	1.3	0.7	2.2	18	1.7	1	2.7	17	1.6	0.9	2.6	49	1.6	1.2	2.1	20	1.9	1.2	2.9
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Earache (0260)	2	0.2	0	0.7	1	0.1	0	0.5	1	0.1	0	0.5	4	0.1	0	0.3	2	0.2	0	0.7
Neoplasm (1700)	Neoplasm nos (1259)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
Psychiatric (500)	Nervousness (0188)	39	3.7	2.7	5.1	30	2.9	1.9	4.1	35	3.3	2.3	4.6	104	3.3	2.7	4	37	3.5	2.5	4.8
Red blood cell (1210)	Anemia (0544)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
Reproductive female (1420)	Leukorrhea (0654)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	0	0	0	0.3
Resistance mechanism (1830)	Abscess (0887)	1	0.1	0	0.5	2	0.2	0	0.7	3	0.3	0.1	0.8	6	0.2	0.1	0.4	0	0	0	0.3
	Infection (0736)	27	2.6	1.7	3.7	23	2.2	1.4	3.3	18	1.7	1	2.7	68	2.2	1.7	2.7	24	2.3	1.5	3.4
	Infection bacterial (0738)	1	0.1	0	0.5	2	0.2	0	0.7	0	0	0	0.3	3	0.1	0	0.3	1	0.1	0	0.5

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 54 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
	Infection viral (0740)	194	18.5	16.2	21	185	17.6	15.4	20.1	185	17.5	15.3	20	564	17.9	16.6	19.3	205	19.4	17	21.9
	Moniliasis (0741)	7	0.7	0.3	1.4	12	1.1	0.6	2	3	0.3	0.1	0.8	22	0.7	0.4	1.1	5	0.5	0.2	1.1
	Otitis media (0750)	5	0.5	0.2	1.1	11	1	0.5	1.9	3	0.3	0.1	0.8	19	0.6	0.4	0.9	11	1	0.5	1.9
	Upper resp tract infection (0543)	47	4.5	3.3	5.9	38	3.6	2.6	4.9	49	4.6	3.5	6.1	134	4.3	3.6	5	42	4	2.9	5.3
Respiratory system (1100)	Asthma (1367)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Atelectasis (1197)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Bronchitis (0805)	21	2	1.2	3	30	2.9	1.9	4.1	21	2	1.2	3	72	2.3	1.8	2.9	14	1.3	0.7	2.2
	Bronchospasm (0511)	14	1.3	0.7	2.2	9	0.9	0.4	1.6	12	1.1	0.6	2	35	1.1	0.8	1.5	8	0.8	0.3	1.5
	Coughing (0513)	34	3.2	2.3	4.5	25	2.4	1.5	3.5	31	2.9	2	4.1	90	2.9	2.3	3.5	21	2	1.2	3
	Dyspnea (0514)	0	0	0	0.4	1	0.1	0	0.5	1	0.1	0	0.5	2	0.1	0	0.2	1	0.1	0	0.5
	Laryngitis (0521)	1	0.1	0	0.5	3	0.3	0.1	0.8	2	0.2	0	0.7	6	0.2	0.1	0.4	2	0.2	0	0.7
	Pharyngitis (0523)	75	7.2	5.7	8.9	100	9.5	7.8	11.5	82	7.8	6.2	9.6	257	8.2	7.2	9.2	85	8	6.5	9.8
	Pneumonia (0528)	14	1.3	0.7	2.2	25	2.4	1.5	3.5	21	2	1.2	3	60	1.9	1.5	2.4	20	1.9	1.2	2.9
	Respiratory disorder (0536)	0	0	0	0.4	7	0.7	0.3	1.4	1	0.1	0	0.5	8	0.3	0.1	0.5	2	0.2	0	0.7
	Rhinitis (0539)	9	0.9	0.4	1.6	15	1.4	0.8	2.3	13	1.2	0.7	2.1	37	1.2	0.8	1.6	14	1.3	0.7	2.2
	Sputum increased (0541)	3	0.3	0.1	0.8	9	0.9	0.4	1.6	2	0.2	0	0.7	14	0.4	0.2	0.7	3	0.3	0.1	0.8
Secondary term (2000)	Varicella (1516)	2	0.2	0	0.7	1	0.1	0	0.5	1	0.1	0	0.5	4	0.1	0	0.3	4	0.4	0.1	1
Skin and appendages (100)	Alopecia (0002)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Dermatitis (0007)	2	0.2	0	0.7	4	0.4	0.1	1	5	0.5	0.2	1.1	11	0.3	0.2	0.6	0	0	0	0.3
	Dermatitis fungal (0009)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Furunculosis (0016)	3	0.3	0.1	0.8	1	0.1	0	0.5	1	0.1	0	0.5	5	0.2	0.1	0.4	0	0	0	0.3

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 54 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
	Photosensitivity reaction (0022)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Pruritus (0024)	0	0	0	0.4	3	0.3	0.1	0.8	2	0.2	0	0.7	5	0.2	0.1	0.4	0	0	0	0.3
	Rash (0027)	1	0.1	0	0.5	1	0.1	0	0.5	0	0	0	0.3	2	0.1	0	0.2	0	0	0	0.3
	Rash erythematous (0028)	2	0.2	0	0.7	1	0.1	0	0.5	0	0	0	0.3	3	0.1	0	0.3	1	0.1	0	0.5
	Rash maculo-papular (0030)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	1	0.1	0	0.5
	Rash pustular (0032)	0	0	0	0.4	2	0.2	0	0.7	3	0.3	0.1	0.8	5	0.2	0.1	0.4	2	0.2	0	0.7
	Seborrhea (0033)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Skin disorder (0037)	6	0.6	0.2	1.2	8	0.8	0.3	1.5	10	0.9	0.5	1.7	24	0.8	0.5	1.1	10	0.9	0.5	1.7
	Sweat gland disorder (1166)	1	0.1	0	0.5	1	0.1	0	0.5	2	0.2	0	0.7	4	0.1	0	0.3	0	0	0	0.3
Urinary system (1300)	Dysuria (0601)	0	0	0	0.4	1	0.1	0	0.5	2	0.2	0	0.7	3	0.1	0	0.3	0	0	0	0.3
	Urinary tract infection (0628)	0	0	0	0.4	0	0	0	0.4	2	0.2	0	0.7	2	0.1	0	0.2	3	0.3	0.1	0.8
Vision (431)	Blepharitis (1007)	1	0.1	0	0.5	0	0	0	0.4	1	0.1	0	0.5	2	0.1	0	0.2	0	0	0	0.3
	Conjunctivitis (0238)	13	1.2	0.7	2.1	13	1.2	0.7	2.1	9	0.9	0.4	1.6	35	1.1	0.8	1.5	10	0.9	0.5	1.7
White cell and reticuloendothelial system (1220)	Lymphadenopathy cervical (0578)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	0	0	0	0.3

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 55: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		2	0.2	0	0.7	0	0	0	0.4	0	0	0	0.3	2	0.1	0	0.2	4	0.4	0.1	1
Application site (1820)	Injection site reaction (0058)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Fever (0725)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Pallor (0220)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Respiratory system (1100)	Bronchitis (0805)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3

Notes: D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 56: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		15	1.4	0.8	2.3	27	2.6	1.7	3.7	14	1.3	0.7	2.2	56	1.8	1.3	2.3	18	1.7	1	2.7
Application site (1820)	Dermatitis contact (0049)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Allergic reaction (0712)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Death, nos (0722)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	0	0	0	0.3
	Edema generalised (0400)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Fever (0725)	0	0	0	0.4	2	0.2	0	0.7	1	0.1	0	0.5	3	0.1	0	0.3	0	0	0	0.3
	Pallor (0220)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Central and peripheral nervous system (410)	Fever convulsions (1357)	1	0.1	0	0.5	0	0	0	0.4	1	0.1	0	0.5	2	0.1	0	0.2	0	0	0	0.3
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Gastrointestinal system (600)	Abdominal pain (0268)	2	0.2	0	0.7	3	0.3	0.1	0.8	1	0.1	0	0.5	6	0.2	0.1	0.4	0	0	0	0.3
	Anorexia (0165)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Constipation (0204)	0	0	0	0.4	1	0.1	0	0.5	1	0.1	0	0.5	2	0.1	0	0.2	0	0	0	0.3
	Gastroenteritis (0293)	3	0.3	0.1	0.8	5	0.5	0.2	1.1	1	0.1	0	0.5	9	0.3	0.1	0.5	4	0.4	0.1	1
	Gastrointestinal disorder nos (1262)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	1	0.1	0	0.5
Psychiatric (500)	Nervousness (0188)	1	0.1	0	0.5	1	0.1	0	0.5	1	0.1	0	0.5	3	0.1	0	0.3	0	0	0	0.3

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 56 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Resistance mechanism (1830)	Infection (0736)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	1	0.1	0	0.5
	Moniliasis (0741)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
Respiratory system (1100)	Asthma (1367)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Bronchitis (0805)	2	0.2	0	0.7	4	0.4	0.1	1	0	0	0	0.3	6	0.2	0.1	0.4	0	0	0	0.3
	Pharyngitis (0523)	3	0.3	0.1	0.8	7	0.7	0.3	1.4	2	0.2	0	0.7	12	0.4	0.2	0.7	2	0.2	0	0.7
	Pneumonia (0528)	5	0.5	0.2	1.1	8	0.8	0.3	1.5	6	0.6	0.2	1.2	19	0.6	0.4	0.9	6	0.6	0.2	1.2

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 57: Percentage of subjects with gastrointestinal symptoms (unsolicited symptoms), from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)		**HRV_4.7 N = 538**				**HRV_5.2 N = 540**				**HRV_5.8 N = 540**				**Pooled HRV groups N = 1618**				**Placebo N = 537**			
				95% CI				**95% CI**				**95% CI**				**95% CI**				**95% CI**	
		s	**%**	**LL**	**UL**	**s**	**%**	**LL**	**UL**	**s**	**%**	**LL**	**UL**	**s**	**%**	**LL**	**UL**	**s**	**%**	**LL**	**UL**
Gastrointestinal system (600)	Any	68	12.6	10	15.7	69	12.8	10.1	15.9	55	10.2	7.8	13.1	192	11.9	10.3	13.5	69	12.8	10.1	16
	Related	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.2	0	0.0	0.0	0.7
	Grade 3	6	1.1	0.4	2.4	9	1.7	0.8	3.1	3	0.6	0.1	1.6	18	1.1	0.7	1.8	5	0.9	0.3	2.2

Notes: N = number of subjects having received at least one dose
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 58: Percentage of doses with gastrointestinal symptoms (unsolicited symptoms), from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)		HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Gastrointestinal system (600)	Any	80	7.6	6.1	9.4	81	7.7	6.2	9.5	68	6.4	5	8.1	229	7.3	6.4	8.2	75	7.1	5.6	8.8
	Related	0	0.0	0.0	0.4	0	0.0	0.0	0.4	0	0.0	0.0	0.3	0	0.0	0.0	0.1	0	0.0	0.0	0.3
	Grade 3	6	0.6	0.2	1.2	9	0.9	0.4	1.6	3	0.3	0.1	0.8	18	0.6	0.3	0.9	5	0.5	0.2	1.1

Notes: D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 59: Number and percentage of doses and of subjects who took at least one concomitant medication from Day 0 to Day 14 after vaccination by type (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

	Overall/dose											
	HRV_4.7 (N=1048)				HRV_5.2 (N=1049)				HRV_5.8 (N=1055)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL			LL	UL
Any medication	652	62.2	59.2	65.2	684	65.2	62.2	68.1	663	62.8	59.8	65.8
Any antipyretic	640	61.1	58.0	64.0	664	63.3	60.3	66.2	647	61.3	58.3	64.3
Prophylactic antipyretic	124	11.8	9.9	13.9	134	12.8	10.8	14.9	130	12.3	10.4	14.5
Any antibiotic	25	2.4	1.5	3.5	43	4.1	3.0	5.5	26	2.5	1.6	3.6

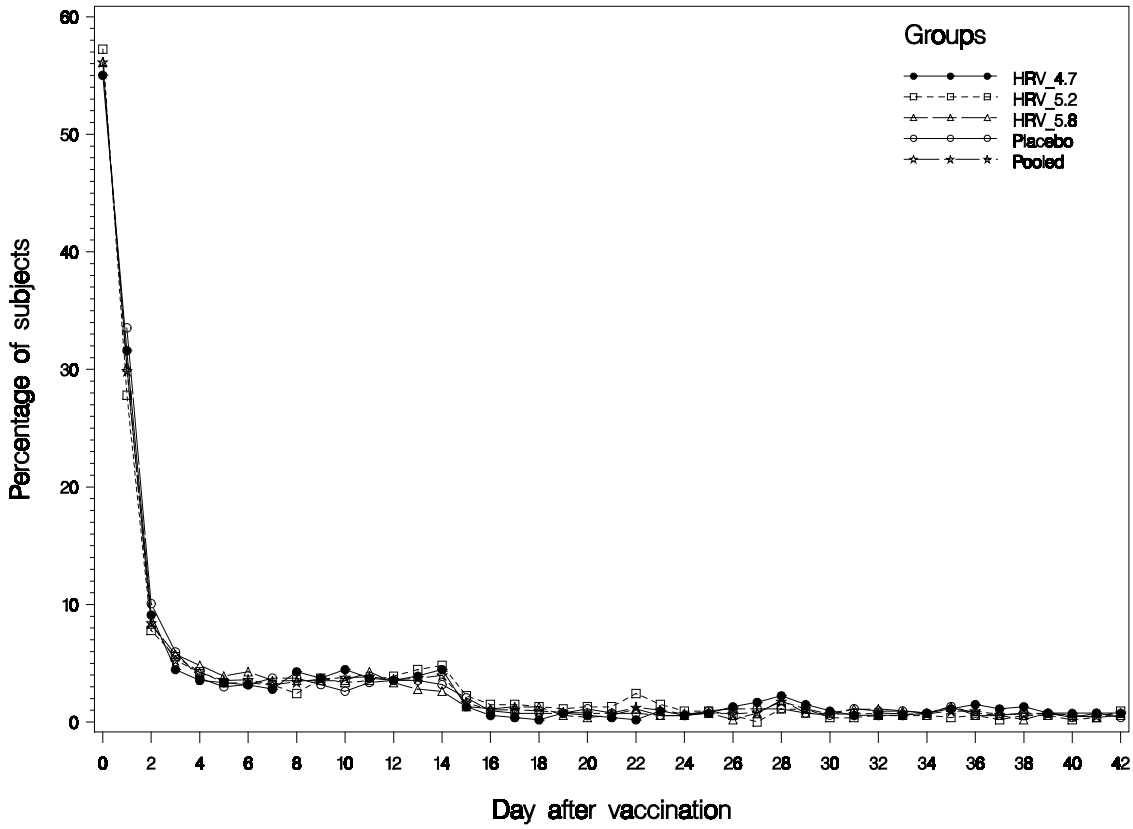
	Pooled HRV groups (N=3152)				Placebo (N=1059)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL
Any medication	1999	63.4	61.7	65.1	700	66.1	63.2	69.0
Any antipyretic	1951	61.9	60.2	63.6	682	64.4	61.4	67.3
Prophylactic antipyretic	388	12.3	11.2	13.5	130	12.3	10.4	14.4
Any antibiotic	94	3.0	2.4	3.6	30	2.8	1.9	4.0

	Overall/subject											
	HRV $10^{4.7}$ (N=538)				HRV $10^{5.2}$ (N=540)				HRV $10^{5.8}$ (N=540)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL			LL	UL
Any medication	428	79.6	75.9	82.9	446	82.6	79.1	85.7	430	79.6	76.0	82.9
Any antipyretic	425	79.0	75.3	82.4	438	81.1	77.6	84.3	422	78.1	74.4	81.6
Prophylactic antipyretic	98	18.2	15.0	21.7	111	20.6	17.2	24.2	100	18.5	15.3	22.1
Any antibiotic	25	4.6	3.0	6.8	41	7.6	5.5	10.2	25	4.6	3.0	6.8

	Pooled HRV groups (N=1618)				Placebo (N=537)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL
Any medication	1304	80.6	78.6	82.5	446	83.1	79.6	86.1
Any antipyretic	1285	79.4	77.4	81.4	438	81.6	78.0	84.8
Prophylactic antipyretic	309	19.1	17.2	21.1	102	19.0	15.8	22.6
Any antibiotic	91	5.6	4.6	6.9	28	5.2	3.5	7.4

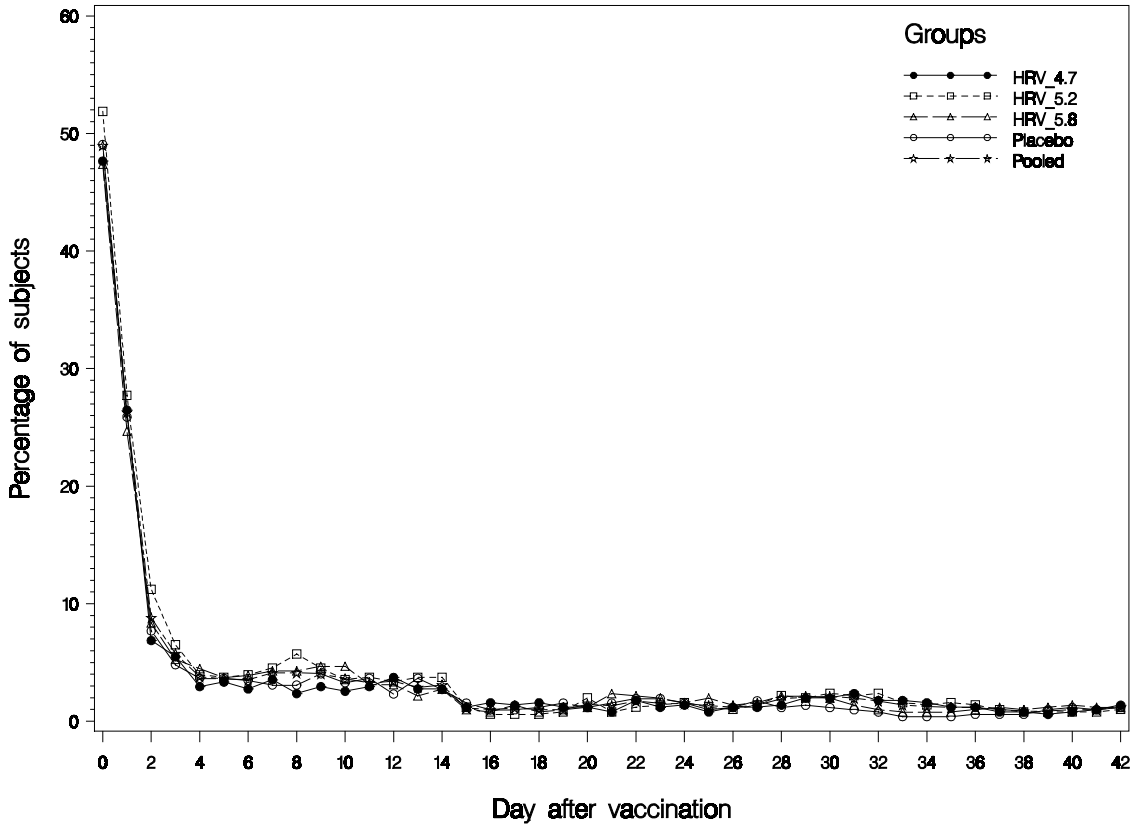
Notes: For overall/dose:
N = total number of doses administered
n/% = number/percentage of doses with at least one specified concomitant medication, from Day 0 to Day 14.
For Overall/subject: N= total number of subjects having received at least one dose
n/% = total number/percentage of subject having who started taking the specified concomitant medication at least once after the considered dose, from Day 0 to Day 14
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 60: Percentage of subjects who took antipyretics after Dose 1, by day from Day 0 to Day 42 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



pooled = pooled HRV groups

Supplement 61: Percentage of subjects who took antipyretics after Dose 2, by day from Day 0 to Day 42 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



pooled = pooled HRV groups

Supplement 62: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	194	187	96.4	92.7	98.5
	HRV_5.2	196	191	97.4	94.1	99.2
	HRV_5.8	194	192	99.0	96.3	99.9
	Pooled HRV groups	584	570	97.6	96.0	98.7
	Placebo	194	191	98.5	95.5	99.7
Dose 2	**HRV_4.7**	187	169	90.4	85.2	94.2
	HRV_5.2	183	172	94.0	89.5	97.0
	HRV_5.8	192	181	94.3	90.0	97.1
	Pooled HRV groups	562	522	92.9	90.4	94.9
	Placebo	191	171	89.5	84.3	93.5
Overall/dose	**HRV_4.7**	381	356	93.4	90.5	95.7
	HRV_5.2	379	363	95.8	93.2	97.6
	HRV_5.8	386	373	96.6	94.3	98.2
	Pooled HRV groups	1146	1092	95.3	93.9	96.4
	Placebo	385	362	94.0	91.2	96.2
Overall/subject	**HRV_4.7**	194	191	98.5	95.5	99.7
	HRV_5.2	196	193	98.5	95.6	99.7
	HRV_5.8	194	194	100.0	98.1	100.0
	Pooled HRV groups	584	578	99.0	97.8	99.6
	Placebo	194	192	99.0	96.3	99.9

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 63: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	101	92	91.1	83.8	95.8
	HRV_5.2	101	94	93.1	86.2	97.2
	HRV_5.8	102	95	93.1	86.4	97.2
	Pooled HRV groups	304	281	92.4	88.9	95.1
	Placebo	101	95	94.1	87.5	97.8
Dose 2	**HRV_4.7**	88	73	83.0	73.4	90.1
	HRV_5.2	95	83	87.4	79.0	93.3
	HRV_5.8	90	81	90.0	81.9	95.3
	Pooled HRV groups	273	237	86.8	82.2	90.6
	Placebo	97	84	86.6	78.2	92.7
Overall/dose	**HRV_4.7**	189	165	87.3	81.7	91.7
	HRV_5.2	196	177	90.3	85.3	94.1
	HRV_5.8	192	176	91.7	86.8	95.2
	Pooled HRV groups	577	518	89.8	87.0	92.1
	Placebo	198	179	90.4	85.4	94.1
Overall/subject	**HRV_4.7**	101	94	93.1	86.2	97.2
	HRV_5.2	101	96	95.0	88.8	98.4
	HRV_5.8	102	97	95.1	88.9	98.4
	Pooled HRV groups	304	287	94.4	91.2	96.7
	Placebo	101	98	97.0	91.6	99.4

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 64: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	243	211	86.8	81.9	90.8
	HRV_5.2	243	206	84.8	79.6	89.0
	HRV_5.8	244	208	85.2	80.2	89.4
	Pooled HRV groups	730	625	85.6	82.9	88.1
	Placebo	242	214	88.4	83.7	92.2
Dose 2	**HRV_4.7**	235	195	83.0	77.6	87.6
	HRV_5.2	231	194	84.0	78.6	88.5
	HRV_5.8	233	189	81.1	75.5	85.9
	Pooled HRV groups	699	578	82.7	79.7	85.4
	Placebo	234	202	86.3	81.2	90.5
Overall/dose	**HRV_4.7**	478	406	84.9	81.4	88.0
	HRV_5.2	474	400	84.4	80.8	87.5
	HRV_5.8	477	397	83.2	79.6	86.5
	Pooled HRV groups	1429	1203	84.2	82.2	86.0
	Placebo	476	416	87.4	84.1	90.2
Overall/subject	**HRV_4.7**	243	229	94.2	90.5	96.8
	HRV_5.2	243	227	93.4	89.5	96.2
	HRV_5.8	244	224	91.8	87.6	94.9
	Pooled HRV groups	730	680	93.2	91.1	94.9
	Placebo	242	231	95.5	92.0	97.7

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 65: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	194	29	14.9	10.2	20.8
	HRV_5.2	196	39	19.9	14.5	26.2
	HRV_5.8	194	45	23.2	17.5	29.8
	Pooled HRV groups	584	113	19.3	16.2	22.8
	Placebo	194	43	22.2	16.5	28.7
Dose 2	**HRV_4.7**	187	38	20.3	14.8	26.8
	HRV_5.2	183	40	21.9	16.1	28.6
	HRV_5.8	192	37	19.3	13.9	25.6
	Pooled HRV groups	562	115	20.5	17.2	24.0
	Placebo	191	34	17.8	12.7	24.0
Overall/dose	**HRV_4.7**	381	67	17.6	13.9	21.8
	HRV_5.2	379	79	20.8	16.9	25.3
	HRV_5.8	386	82	21.2	17.3	25.7
	Pooled HRV groups	1146	228	19.9	17.6	22.3
	Placebo	385	77	20.0	16.1	24.3
Overall/subject	**HRV_4.7**	194	60	30.9	24.5	37.9
	HRV_5.2	196	72	36.7	30.0	43.9
	HRV_5.8	194	70	36.1	29.3	43.3
	Pooled HRV groups	584	202	34.6	30.7	38.6
	Placebo	194	65	33.5	26.9	40.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 66: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	101	16	15.8	9.3	24.4
	HRV_5.2	101	13	12.9	7.0	21.0
	HRV_5.8	102	13	12.7	7.0	20.8
	Pooled HRV groups	304	42	13.8	10.1	18.2
	Placebo	101	9	8.9	4.2	16.2
Dose 2	**HRV_4.7**	88	5	5.7	1.9	12.8
	HRV_5.2	95	15	15.8	9.1	24.7
	HRV_5.8	90	12	13.3	7.1	22.1
	Pooled HRV groups	273	32	11.7	8.2	16.1
	Placebo	97	12	12.4	6.6	20.6
Overall/dose	**HRV_4.7**	189	21	11.1	7.0	16.5
	HRV_5.2	196	28	14.3	9.7	20.0
	HRV_5.8	192	25	13.0	8.6	18.6
	Pooled HRV groups	577	74	12.8	10.2	15.8
	Placebo	198	21	10.6	6.7	15.8
Overall/subject	**HRV_4.7**	101	19	18.8	11.7	27.8
	HRV_5.2	101	27	26.7	18.4	36.5
	HRV_5.8	102	20	19.6	12.4	28.6
	Pooled HRV groups	304	66	21.7	17.2	26.8
	Placebo	101	19	18.8	11.7	27.8

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 67: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	243	69	28.4	22.8	34.5
	HRV_5.2	243	76	31.3	25.5	37.5
	HRV_5.8	244	82	33.6	27.7	39.9
	Pooled HRV groups	730	227	31.1	27.8	34.6
	Placebo	242	77	31.8	26.0	38.1
Dose 2	**HRV_4.7**	235	62	26.4	20.9	32.5
	HRV_5.2	231	56	24.2	18.9	30.3
	HRV_5.8	233	65	27.9	22.2	34.1
	Pooled HRV groups	699	183	26.2	23.0	29.6
	Placebo	234	58	24.8	19.4	30.8
Overall/dose	**HRV_4.7**	478	131	27.4	23.5	31.6
	HRV_5.2	474	132	27.8	23.9	32.1
	HRV_5.8	477	147	30.8	26.7	35.2
	Pooled HRV groups	1429	410	28.7	26.4	31.1
	Placebo	476	135	28.4	24.4	32.6
Overall/subject	**HRV_4.7**	243	101	41.6	35.3	48.0
	HRV_5.2	243	105	43.2	36.9	49.7
	HRV_5.8	244	106	43.4	37.1	49.9
	Pooled HRV groups	730	312	42.7	39.1	46.4
	Placebo	242	106	43.8	37.5	50.3

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N = number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 68: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	194	184	94.8	90.7	97.5
	HRV_5.2	196	185	94.4	90.2	97.2
	HRV_5.8	194	181	93.3	88.8	96.4
	Pooled HRV groups	584	550	94.2	92.0	95.9
	Placebo	194	183	94.3	90.1	97.1
Dose 2	**HRV_4.7**	187	150	80.2	73.8	85.7
	HRV_5.2	183	152	83.1	76.8	88.2
	HRV_5.8	192	164	85.4	79.6	90.1
	Pooled HRV groups	562	466	82.9	79.5	85.9
	Placebo	191	142	74.3	67.5	80.4
Overall/dose	**HRV_4.7**	381	334	87.7	83.9	90.8
	HRV_5.2	379	337	88.9	85.3	91.9
	HRV_5.8	386	345	89.4	85.9	92.3
	Pooled HRV groups	1146	1016	88.7	86.7	90.4
	Placebo	385	325	84.4	80.4	87.9
Overall/Subject	**HRV_4.7**	194	190	97.9	94.8	99.4
	HRV_5.2	196	192	98.0	94.9	99.4
	HRV_5.8	194	192	99.0	96.3	99.9
	Pooled HRV groups	584	574	98.3	96.9	99.2
	Placebo	194	184	94.8	90.7	97.5

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 69: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	101	90	89.1	81.3	94.4
	HRV_5.2	101	93	92.1	85.0	96.5
	HRV_5.8	102	90	88.2	80.4	93.8
	Pooled HRV groups	304	273	89.8	85.8	93.0
	Placebo	101	92	91.1	83.8	95.8
Dose 2	**HRV_4.7**	88	68	77.3	67.1	85.5
	HRV_5.2	95	80	84.2	75.3	90.9
	HRV_5.8	90	76	84.4	75.3	91.2
	Pooled HRV groups	273	224	82.1	77.0	86.4
	Placebo	97	81	83.5	74.6	90.3
Overall/dose	**HRV_4.7**	189	158	83.6	77.5	88.6
	HRV_5.2	196	173	88.3	82.9	92.4
	HRV_5.8	192	166	86.5	80.8	91.0
	Pooled HRV groups	577	497	86.1	83.0	88.9
	Placebo	198	173	87.4	81.9	91.7
Overall/subject	**HRV_4.7**	101	94	93.1	86.2	97.2
	HRV_5.2	101	95	94.1	87.5	97.8
	HRV_5.8	102	95	93.1	86.4	97.2
	Pooled HRV groups	304	284	93.4	90.0	95.9
	Placebo	101	96	95.0	88.8	98.4

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 70: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	243	1	0.4	0.0	2.3
	HRV_5.2	243	0	0.0	0.0	1.5
	HRV_5.8	244	0	0.0	0.0	1.5
	Pooled HRV groups	730	1	0.1	0.0	0.8
	Placebo	242	1	0.4	0.0	2.3
Dose 2	**HRV_4.7**	235	0	0.0	0.0	1.6
	HRV_5.2	231	2	0.9	0.1	3.1
	HRV_5.8	233	0	0.0	0.0	1.6
	Pooled HRV groups	699	2	0.3	0.0	1.0
	Placebo	234	0	0.0	0.0	1.6
Overall/dose	**HRV_4.7**	478	1	0.2	0.0	1.2
	HRV_5.2	474	2	0.4	0.1	1.5
	HRV_5.8	477	0	0.0	0.0	0.8
	Pooled HRV groups	1429	3	0.2	0.0	0.6
	Placebo	476	1	0.2	0.0	1.2
Overall/subject	**HRV_4.7**	243	1	0.4	0.0	2.3
	HRV_5.2	243	2	0.8	0.1	2.9
	HRV_5.8	244	0	0.0	0.0	1.5
	Pooled HRV groups	730	3	0.4	0.1	1.2
	Placebo	242	1	0.4	0.0	2.3

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/%= number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71: Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		1											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		194				196				194			
COUGH	Total	125	64.4	57.3	71.2	131	66.8	59.8	73.4	119	61.3	54.1	68.2
	Grade 2*3	54	27.8	21.7	34.7	42	21.4	15.9	27.8	56	28.9	22.6	35.8
	Grade 3	7	3.6	1.5	7.3	9	4.6	2.1	8.5	10	5.2	2.5	9.3
	Related	66	34.0	27.4	41.2	62	31.6	25.2	38.6	50	25.8	19.8	32.5
DIARRHEA	Total	22	11.3	7.2	16.7	24	12.2	8.0	17.7	29	14.9	10.2	20.8
	Grade 2*3	12	6.2	3.2	10.6	15	7.7	4.3	12.3	15	7.7	4.4	12.4
	Grade 3	5	2.6	0.8	5.9	7	3.6	1.4	7.2	6	3.1	1.1	6.6
	Related	11	5.7	2.9	9.9	14	7.1	4.0	11.7	20	10.3	6.4	15.5
IRRITABILITY	Total	164	84.5	78.7	89.3	160	81.6	75.5	86.8	167	86.1	80.4	90.6
	Grade 2*3	117	60.3	53.1	67.2	93	47.4	40.3	54.7	121	62.4	55.1	69.2
	Grade 3	17	8.8	5.2	13.7	21	10.7	6.8	15.9	23	11.9	7.7	17.3
	Related	156	80.4	74.1	85.8	155	79.1	72.7	84.6	161	83.0	76.9	88.0
LOSS OF APPETITE	Total	54	27.8	21.7	34.7	57	29.1	22.8	36.0	58	29.9	23.5	36.9
	Grade 2*3	24	12.4	8.1	17.8	18	9.2	5.5	14.1	24	12.4	8.1	17.8
	Grade 3	4	2.1	0.6	5.2	1	0.5	0.0	2.8	1	0.5	0.0	2.8
	Related	39	20.1	14.7	26.4	42	21.4	15.9	27.8	44	22.7	17.0	29.2
FEVER	Total	148	76.3	69.7	82.1	144	73.5	66.7	79.5	140	72.2	65.3	78.3
	Grade 2*3	75	38.7	31.8	45.9	66	33.7	27.1	40.8	74	38.1	31.3	45.4
	Grade 3	2	1.0	0.1	3.7	3	1.5	0.3	4.4	4	2.1	0.6	5.2
	Related	144	74.2	67.5	80.2	137	69.9	63.0	76.2	132	68.0	61.0	74.5
VOMITING	Total	46	23.7	17.9	30.3	53	27.0	21.0	33.8	47	24.2	18.4	30.9
	Grade 2*3	15	7.7	4.4	12.4	29	14.8	10.1	20.6	20	10.3	6.4	15.5
	Grade 3	5	2.6	0.8	5.9	9	4.6	2.1	8.5	10	5.2	2.5	9.3
	Related	31	16.0	11.1	21.9	30	15.3	10.6	21.1	27	13.9	9.4	19.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		**1**							
Group		**Pooled HRV groups**				**Placebo**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
N		584				194			
COUGH	**Total**	375	64.2	60.2	68.1	133	68.6	61.5	75.0
	Grade 2*3	152	26.0	22.5	29.8	61	31.4	25.0	38.5
	Grade 3	26	4.5	2.9	6.5	6	3.1	1.1	6.6
	Related	178	30.5	26.8	34.4	61	31.4	25.0	38.5
DIARRHEA	**Total**	75	12.8	10.2	15.8	28	14.4	9.8	20.2
	Grade 2*3	42	7.2	5.2	9.6	16	8.2	4.8	13.0
	Grade 3	18	3.1	1.8	4.8	6	3.1	1.1	6.6
	Related	45	7.7	5.7	10.2	13	6.7	3.6	11.2
IRRITABILITY	**Total**	491	84.1	80.9	87.0	170	87.6	82.2	91.9
	Grade 2*3	331	56.7	52.5	60.7	115	59.3	52.0	66.3
	Grade 3	61	10.4	8.1	13.2	27	13.9	9.4	19.6
	Related	472	80.8	77.4	83.9	165	85.1	79.2	89.8
LOSS OF APPETITE	**Total**	169	28.9	25.3	32.8	66	34.0	27.4	41.2
	Grade 2*3	66	11.3	8.8	14.2	27	13.9	9.4	19.6
	Grade 3	6	1.0	0.4	2.2	2	1.0	0.1	3.7
	Related	125	21.4	18.1	25.0	54	27.8	21.7	34.7
FEVER	**Total**	432	74.0	70.2	77.5	143	73.7	66.9	79.8
	Grade 2*3	215	36.8	32.9	40.9	71	36.6	29.8	43.8
	Grade 3	9	1.5	0.7	2.9	6	3.1	1.1	6.6
	Related	413	70.7	66.8	74.4	137	70.6	63.7	76.9
VOMITING	**Total**	146	25.0	21.5	28.7	49	25.3	19.3	32.0
	Grade 2*3	64	11.0	8.5	13.8	21	10.8	6.8	16.1
	Grade 3	24	4.1	2.7	6.1	5	2.6	0.8	5.9
	Related	88	15.1	12.3	18.2	37	19.1	13.8	25.3

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		2											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		187				183				192			
COUGH	Total	125	66.8	59.6	73.5	133	72.7	65.6	79.0	129	67.2	60.1	73.8
	Grade 2*3	67	35.8	29.0	43.2	60	32.8	26.0	40.1	58	30.2	23.8	37.2
	Grade 3	15	8.0	4.6	12.9	16	8.7	5.1	13.8	13	6.8	3.7	11.3
	Related	61	32.6	26.0	39.8	66	36.1	29.1	43.5	70	36.5	29.6	43.7
DIARRHEA	Total	31	16.6	11.6	22.7	28	15.3	10.4	21.3	28	14.6	9.9	20.4
	Grade 2*3	23	12.3	8.0	17.9	21	11.5	7.2	17.0	15	7.8	4.4	12.6
	Grade 3	5	2.7	0.9	6.1	11	6.0	3.0	10.5	6	3.1	1.2	6.7
	Related	17	9.1	5.4	14.2	20	10.9	6.8	16.4	13	6.8	3.7	11.3
IRRITABILITY	Total	120	64.2	56.8	71.0	121	66.1	58.8	72.9	123	64.1	56.8	70.8
	Grade 2*3	64	34.2	27.5	41.5	61	33.3	26.6	40.7	65	33.9	27.2	41.0
	Grade 3	16	8.6	5.0	13.5	12	6.6	3.4	11.2	6	3.1	1.2	6.7
	Related	112	59.9	52.5	67.0	113	61.7	54.3	68.8	117	60.9	53.7	67.9
LOSS OF APPETITE	Total	56	29.9	23.5	37.1	45	24.6	18.5	31.5	47	24.5	18.6	31.2
	Grade 2*3	27	14.4	9.7	20.3	24	13.1	8.6	18.9	18	9.4	5.7	14.4
	Grade 3	3	1.6	0.3	4.6	6	3.3	1.2	7.0	3	1.6	0.3	4.5
	Related	38	20.3	14.8	26.8	34	18.6	13.2	25.0	29	15.1	10.4	21.0
FEVER	Total	113	60.4	53.0	67.5	89	48.6	41.2	56.1	116	60.4	53.1	67.4
	Grade 2*3	58	31.0	24.5	38.2	46	25.1	19.0	32.1	58	30.2	23.8	37.2
	Grade 3	7	3.7	1.5	7.6	6	3.3	1.2	7.0	7	3.6	1.5	7.4
	Related	99	52.9	45.5	60.3	79	43.2	35.9	50.7	106	55.2	47.9	62.4
VOMITING	Total	33	17.6	12.5	23.9	36	19.7	14.2	26.2	34	17.7	12.6	23.9
	Grade 2*3	14	7.5	4.2	12.2	22	12.0	7.7	17.6	17	8.9	5.2	13.8
	Grade 3	9	4.8	2.2	8.9	10	5.5	2.7	9.8	9	4.7	2.2	8.7
	Related	23	12.3	8.0	17.9	20	10.9	6.8	16.4	20	10.4	6.5	15.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		2							
		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		562				191			
COUGH	Total	387	68.9	64.9	72.7	138	72.3	65.3	78.5
	Grade 2*3	185	32.9	29.0	37.0	67	35.1	28.3	42.3
	Grade 3	44	7.8	5.7	10.4	13	6.8	3.7	11.4
	Related	197	35.1	31.1	39.2	60	31.4	24.9	38.5
DIARRHEA	Total	87	15.5	12.6	18.7	28	14.7	10.0	20.5
	Grade 2*3	59	10.5	8.1	13.3	22	11.5	7.4	16.9
	Grade 3	22	3.9	2.5	5.9	10	5.2	2.5	9.4
	Related	50	8.9	6.7	11.6	11	5.8	2.9	10.1
IRRITABILITY	Total	364	64.8	60.7	68.7	108	56.5	49.2	63.7
	Grade 2*3	190	33.8	29.9	37.9	59	30.9	24.4	38.0
	Grade 3	34	6.0	4.2	8.4	8	4.2	1.8	8.1
	Related	342	60.9	56.7	64.9	100	52.4	45.0	59.6
LOSS OF APPETITE	Total	148	26.3	22.7	30.2	46	24.1	18.2	30.8
	Grade 2*3	69	12.3	9.7	15.3	21	11.0	6.9	16.3
	Grade 3	12	2.1	1.1	3.7	1	0.5	0.0	2.9
	Related	101	18.0	14.9	21.4	32	16.8	11.8	22.8
FEVER	Total	318	56.6	52.4	60.7	101	52.9	45.5	60.1
	Grade 2*3	162	28.8	25.1	32.8	44	23.0	17.3	29.7
	Grade 3	20	3.6	2.2	5.4	7	3.7	1.5	7.4
	Related	284	50.5	46.3	54.7	82	42.9	35.8	50.3
VOMITING	Total	103	18.3	15.2	21.8	26	13.6	9.1	19.3
	Grade 2*3	53	9.4	7.1	12.2	12	6.3	3.3	10.7
	Grade 3	28	5.0	3.3	7.1	6	3.1	1.2	6.7
	Related	63	11.2	8.7	14.1	16	8.4	4.9	13.2

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/Dose											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		381				379				386			
COUGH	Total	250	65.6	60.6	70.4	264	69.7	64.8	74.2	248	64.2	59.2	69.0
	Grade 2*3	121	31.8	27.1	36.7	102	26.9	22.5	31.7	114	29.5	25.0	34.4
	Grade 3	22	5.8	3.7	8.6	25	6.6	4.3	9.6	23	6.0	3.8	8.8
	Related	127	33.3	28.6	38.3	128	33.8	29.0	38.8	120	31.1	26.5	36.0
DIARRHEA	Total	53	13.9	10.6	17.8	52	13.7	10.4	17.6	57	14.8	11.4	18.7
	Grade 2*3	35	9.2	6.5	12.5	36	9.5	6.7	12.9	30	7.8	5.3	10.9
	Grade 3	10	2.6	1.3	4.8	18	4.7	2.8	7.4	12	3.1	1.6	5.4
	Related	28	7.3	4.9	10.4	34	9.0	6.3	12.3	33	8.5	6.0	11.8
IRRITABILITY	Total	284	74.5	69.9	78.8	281	74.1	69.4	78.5	290	75.1	70.5	79.4
	Grade 2*3	181	47.5	42.4	52.7	154	40.6	35.6	45.8	186	48.2	43.1	53.3
	Grade 3	33	8.7	6.0	11.9	33	8.7	6.1	12.0	29	7.5	5.1	10.6
	Related	268	70.3	65.5	74.9	268	70.7	65.8	75.2	278	72.0	67.3	76.4
LOSS OF APPETITE	Total	110	28.9	24.4	33.7	102	26.9	22.5	31.7	105	27.2	22.8	31.9
	Grade 2*3	51	13.4	10.1	17.2	42	11.1	8.1	14.7	42	10.9	8.0	14.4
	Grade 3	7	1.8	0.7	3.7	7	1.8	0.7	3.8	4	1.0	0.3	2.6
	Related	77	20.2	16.3	24.6	76	20.1	16.1	24.4	73	18.9	15.1	23.2
FEVER	Total	261	68.5	63.6	73.1	233	61.5	56.4	66.4	256	66.3	61.4	71.0
	Grade 2*3	133	34.9	30.1	39.9	112	29.6	25.0	34.4	132	34.2	29.5	39.2
	Grade 3	9	2.4	1.1	4.4	9	2.4	1.1	4.5	11	2.8	1.4	5.0
	Related	243	63.8	58.7	68.6	216	57.0	51.8	62.0	238	61.7	56.6	66.5
VOMITING	Total	79	20.7	16.8	25.2	89	23.5	19.3	28.1	81	21.0	17.0	25.4
	Grade 2*3	29	7.6	5.2	10.7	51	13.5	10.2	17.3	37	9.6	6.8	13.0
	Grade 3	14	3.7	2.0	6.1	19	5.0	3.0	7.7	19	4.9	3.0	7.6
	Related	54	14.2	10.8	18.1	50	13.2	10.0	17.0	47	12.2	9.1	15.9

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/Dose							
		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		1146				385			
COUGH	Total	762	66.5	63.7	69.2	271	70.4	65.6	74.9
	Grade 2*3	337	29.4	26.8	32.1	128	33.2	28.6	38.2
	Grade 3	70	6.1	4.8	7.7	19	4.9	3.0	7.6
	Related	375	32.7	30.0	35.5	121	31.4	26.8	36.3
DIARRHEA	Total	162	14.1	12.2	16.3	56	14.5	11.2	18.5
	Grade 2*3	101	8.8	7.2	10.6	38	9.9	7.1	13.3
	Grade 3	40	3.5	2.5	4.7	16	4.2	2.4	6.7
	Related	95	8.3	6.8	10.0	24	6.2	4.0	9.1
IRRITABILITY	Total	855	74.6	72.0	77.1	278	72.2	67.4	76.6
	Grade 2*3	521	45.5	42.6	48.4	174	45.2	40.1	50.3
	Grade 3	95	8.3	6.8	10.0	35	9.1	6.4	12.4
	Related	814	71.0	68.3	73.6	265	68.8	63.9	73.4
LOSS OF APPETITE	Total	317	27.7	25.1	30.4	112	29.1	24.6	33.9
	Grade 2*3	135	11.8	10.0	13.8	48	12.5	9.3	16.2
	Grade 3	18	1.6	0.9	2.5	3	0.8	0.2	2.3
	Related	226	19.7	17.5	22.1	86	22.3	18.3	26.8
FEVER	Total	750	65.4	62.6	68.2	244	63.4	58.3	68.2
	Grade 2*3	377	32.9	30.2	35.7	115	29.9	25.3	34.7
	Grade 3	29	2.5	1.7	3.6	13	3.4	1.8	5.7
	Related	697	60.8	57.9	63.7	219	56.9	51.8	61.9
VOMITING	Total	249	21.7	19.4	24.2	75	19.5	15.6	23.8
	Grade 2*3	117	10.2	8.5	12.1	33	8.6	6.0	11.8
	Grade 3	52	4.5	3.4	5.9	11	2.9	1.4	5.1
	Related	151	13.2	11.3	15.3	53	13.8	10.5	17.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/Subject											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		194				196				194			
COUGH	Total	158	81.4	75.2	86.7	167	85.2	79.4	89.9	161	83.0	76.9	88.0
	Grade 2*3	90	46.4	39.2	53.7	87	44.4	37.3	51.6	91	46.9	39.7	54.2
	Grade 3	21	10.8	6.8	16.1	24	12.2	8.0	17.7	21	10.8	6.8	16.1
	Related	97	50.0	42.8	57.2	105	53.6	46.3	60.7	100	51.5	44.3	58.8
DIARRHEA	Total	50	25.8	19.8	32.5	45	23.0	17.3	29.5	49	25.3	19.3	32.0
	Grade 2*3	33	17.0	12.0	23.1	34	17.3	12.3	23.4	28	14.4	9.8	20.2
	Grade 3	10	5.2	2.5	9.3	18	9.2	5.5	14.1	11	5.7	2.9	9.9
	Related	28	14.4	9.8	20.2	32	16.3	11.4	22.3	29	14.9	10.2	20.8
IRRITABILITY	Total	174	89.7	84.5	93.6	177	90.3	85.3	94.1	181	93.3	88.8	96.4
	Grade 2*3	134	69.1	62.1	75.5	116	59.2	52.0	66.1	136	70.1	63.1	76.5
	Grade 3	28	14.4	9.8	20.2	30	15.3	10.6	21.1	25	12.9	8.5	18.4
	Related	167	86.1	80.4	90.6	171	87.2	81.7	91.6	178	91.8	87.0	95.2
LOSS OF APPETITE	Total	88	45.4	38.2	52.6	78	39.8	32.9	47.0	82	42.3	35.2	49.6
	Grade 2*3	45	23.2	17.5	29.8	37	18.9	13.7	25.1	37	19.1	13.8	25.3
	Grade 3	7	3.6	1.5	7.3	6	3.1	1.1	6.5	4	2.1	0.6	5.2
	Related	65	33.5	26.9	40.6	62	31.6	25.2	38.6	60	30.9	24.5	37.9
FEVER	Total	171	88.1	82.7	92.3	161	82.1	76.1	87.2	163	84.0	78.1	88.9
	Grade 2*3	111	57.2	49.9	64.3	95	48.5	41.3	55.7	106	54.6	47.4	61.8
	Grade 3	9	4.6	2.1	8.6	9	4.6	2.1	8.5	11	5.7	2.9	9.9
	Related	166	85.6	79.8	90.2	151	77.0	70.5	82.7	157	80.9	74.7	86.2
VOMITING	Total	65	33.5	26.9	40.6	71	36.2	29.5	43.4	66	34.0	27.4	41.2
	Grade 2*3	26	13.4	8.9	19.0	43	21.9	16.4	28.4	35	18.0	12.9	24.2
	Grade 3	13	6.7	3.6	11.2	17	8.7	5.1	13.5	18	9.3	5.6	14.3
	Related	47	24.2	18.4	30.9	43	21.9	16.4	28.4	41	21.1	15.6	27.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/Subject							
		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		584				194			
COUGH	Total	486	83.2	79.9	86.2	171	88.1	82.7	92.3
	Grade 2*3	268	45.9	41.8	50.0	106	54.6	47.4	61.8
	Grade 3	66	11.3	8.8	14.2	19	9.8	6.0	14.9
	Related	302	51.7	47.6	55.8	97	50.0	42.8	57.2
DIARRHEA	Total	144	24.7	21.2	28.4	53	27.3	21.2	34.2
	Grade 2*3	95	16.3	13.4	19.5	37	19.1	13.8	25.3
	Grade 3	39	6.7	4.8	9.0	15	7.7	4.4	12.4
	Related	89	15.2	12.4	18.4	24	12.4	8.1	17.8
IRRITABILITY	Total	532	91.1	88.5	93.3	176	90.7	85.7	94.4
	Grade 2*3	386	66.1	62.1	69.9	133	68.6	61.5	75.0
	Grade 3	83	14.2	11.5	17.3	33	17.0	12.0	23.1
	Related	516	88.4	85.5	90.8	173	89.2	83.9	93.2
LOSS OF APPETITE	Total	248	42.5	38.4	46.6	88	45.4	38.2	52.6
	Grade 2*3	119	20.4	17.2	23.9	42	21.6	16.1	28.1
	Grade 3	17	2.9	1.7	4.6	3	1.5	0.3	4.5
	Related	187	32.0	28.3	36.0	71	36.6	29.8	43.8
FEVER	Total	495	84.8	81.6	87.6	164	84.5	78.7	89.3
	Grade 2*3	312	53.4	49.3	57.5	93	47.9	40.7	55.2
	Grade 3	29	5.0	3.4	7.1	12	6.2	3.2	10.6
	Related	474	81.2	77.8	84.3	155	79.9	73.6	85.3
VOMITING	Total	202	34.6	30.7	38.6	65	33.5	26.9	40.6
	Grade 2*3	104	17.8	14.8	21.2	31	16.0	11.1	21.9
	Grade 3	48	8.2	6.1	10.7	10	5.2	2.5	9.3
	Related	131	22.4	19.1	26.0	49	25.3	19.3	32.0

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72: Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		1											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		101				101				102			
COUGH	Total	54	53.5	43.3	63.5	50	49.5	39.4	59.6	50	49.0	39.0	59.1
	Grade 2*3	13	12.9	7.0	21.0	14	13.9	7.8	22.2	9	8.8	4.1	16.1
	Grade 3	4	4.0	1.1	9.8	1	1.0	0.0	5.4	2	2.0	0.2	6.9
	Related	43	42.6	32.8	52.8	40	39.6	30.0	49.8	41	40.2	30.6	50.4
DIARRHEA	Total	8	7.9	3.5	15.0	7	6.9	2.8	13.8	12	11.8	6.2	19.6
	Grade 2*3	5	5.0	1.6	11.2	6	5.9	2.2	12.5	10	9.8	4.8	17.3
	Grade 3	2	2.0	0.2	7.0	3	3.0	0.6	8.4	2	2.0	0.2	6.9
	Related	5	5.0	1.6	11.2	6	5.9	2.2	12.5	9	8.8	4.1	16.1
IRRITABILITY	Total	83	82.2	73.3	89.1	77	76.2	66.7	84.1	86	84.3	75.8	90.8
	Grade 2*3	27	26.7	18.4	36.5	37	36.6	27.3	46.8	36	35.3	26.1	45.4
	Grade 3	5	5.0	1.6	11.2	5	5.0	1.6	11.2	4	3.9	1.1	9.7
	Related	79	78.2	68.9	85.8	72	71.3	61.4	79.9	80	78.4	69.2	86.0
LOSS OF APPETITE	Total	41	40.6	30.9	50.8	44	43.6	33.7	53.8	38	37.3	27.9	47.4
	Grade 2*3	8	7.9	3.5	15.0	7	6.9	2.8	13.8	11	10.8	5.5	18.5
	Grade 3	0	0.0	0.0	3.6	2	2.0	0.2	7.0	0	0.0	0.0	3.6
	Related	35	34.7	25.5	44.8	36	35.6	26.4	45.8	34	33.3	24.3	43.4
FEVER	Total	64	63.4	53.2	72.7	59	58.4	48.2	68.1	66	64.7	54.6	73.9
	Grade 2*3	28	27.7	19.3	37.5	25	24.8	16.7	34.3	29	28.4	19.9	38.2
	Grade 3	3	3.0	0.6	8.4	2	2.0	0.2	7.0	3	2.9	0.6	8.4
	Related	61	60.4	50.2	70.0	52	51.5	41.3	61.6	57	55.9	45.7	65.7
VOMITING	Total	22	21.8	14.2	31.1	21	20.8	13.4	30.0	19	18.6	11.6	27.6
	Grade 2*3	12	11.9	6.3	19.8	15	14.9	8.6	23.3	11	10.8	5.5	18.5
	Grade 3	5	5.0	1.6	11.2	7	6.9	2.8	13.8	6	5.9	2.2	12.4
	Related	17	16.8	10.1	25.6	16	15.8	9.3	24.4	13	12.7	7.0	20.8

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		**1**							
Group		**Pooled HRV groups**				**Placebo**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
N		**304**				**101**			
COUGH	**Total**	154	50.7	44.9	56.4	55	54.5	44.2	64.4
	Grade 2*3	36	11.8	8.4	16.0	12	11.9	6.3	19.8
	Grade 3	7	2.3	0.9	4.7	0	0.0	0.0	3.6
	Related	124	40.8	35.2	46.5	43	42.6	32.8	52.8
DIARRHEA	**Total**	27	8.9	5.9	12.7	12	11.9	6.3	19.8
	Grade 2*3	21	6.9	4.3	10.4	8	7.9	3.5	15.0
	Grade 3	7	2.3	0.9	4.7	2	2.0	0.2	7.0
	Related	20	6.6	4.1	10.0	10	9.9	4.9	17.5
IRRITABILITY	**Total**	246	80.9	76.0	85.2	85	84.2	75.6	90.7
	Grade 2*3	100	32.9	27.6	38.5	35	34.7	25.5	44.8
	Grade 3	14	4.6	2.5	7.6	3	3.0	0.6	8.4
	Related	231	76.0	70.8	80.7	78	77.2	67.8	85.0
LOSS OF APPETITE	**Total**	123	40.5	34.9	46.2	35	34.7	25.5	44.8
	Grade 2*3	26	8.6	5.7	12.3	7	6.9	2.8	13.8
	Grade 3	2	0.7	0.1	2.4	0	0.0	0.0	3.6
	Related	105	34.5	29.2	40.2	33	32.7	23.7	42.7
FEVER	**Total**	189	62.2	56.5	67.6	58	57.4	47.2	67.2
	Grade 2*3	82	27.0	22.1	32.3	23	22.8	15.0	32.2
	Grade 3	8	2.6	1.1	5.1	2	2.0	0.2	7.0
	Related	170	55.9	50.1	61.6	55	54.5	44.2	64.4
VOMITING	**Total**	62	20.4	16.0	25.4	19	18.8	11.7	27.8
	Grade 2*3	38	12.5	9.0	16.8	12	11.9	6.3	19.8
	Grade 3	18	5.9	3.5	9.2	4	4.0	1.1	9.8
	Related	46	15.1	11.3	19.7	17	16.8	10.1	25.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		2											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		88				95				90			
COUGH	Total	45	51.1	40.2	61.9	52	54.7	44.2	65.0	54	60.0	49.1	70.2
	Grade 2*3	6	6.8	2.5	14.3	15	15.8	9.1	24.7	13	14.4	7.9	23.4
	Grade 3	1	1.1	0.0	6.2	3	3.2	0.7	9.0	2	2.2	0.3	7.8
	Related	36	40.9	30.5	51.9	43	45.3	35.0	55.8	39	43.3	32.9	54.2
DIARRHEA	Total	4	4.5	1.3	11.2	5	5.3	1.7	11.9	12	13.3	7.1	22.1
	Grade 2*3	3	3.4	0.7	9.6	1	1.1	0.0	5.7	10	11.1	5.5	19.5
	Grade 3	1	1.1	0.0	6.2	0	0.0	0.0	3.8	4	4.4	1.2	11.0
	Related	2	2.3	0.3	8.0	3	3.2	0.7	9.0	8	8.9	3.9	16.8
IRRITABILITY	Total	63	71.6	61.0	80.7	69	72.6	62.5	81.3	67	74.4	64.2	83.1
	Grade 2*3	24	27.3	18.3	37.8	27	28.4	19.6	38.6	32	35.6	25.7	46.3
	Grade 3	4	4.5	1.3	11.2	3	3.2	0.7	9.0	4	4.4	1.2	11.0
	Related	56	63.6	52.7	73.6	60	63.2	52.6	72.8	60	66.7	55.9	76.3
LOSS OF APPETITE	Total	25	28.4	19.3	39.0	26	27.4	18.7	37.5	30	33.3	23.7	44.1
	Grade 2*3	12	13.6	7.2	22.6	7	7.4	3.0	14.6	6	6.7	2.5	13.9
	Grade 3	2	2.3	0.3	8.0	1	1.1	0.0	5.7	0	0.0	0.0	4.0
	Related	21	23.9	15.4	34.1	20	21.1	13.4	30.6	24	26.7	17.9	37.0
FEVER	Total	45	51.1	40.2	61.9	54	56.8	46.3	67.0	44	48.9	38.2	59.7
	Grade 2*3	13	14.8	8.1	23.9	26	27.4	18.7	37.5	19	21.1	13.2	31.0
	Grade 3	1	1.1	0.0	6.2	5	5.3	1.7	11.9	2	2.2	0.3	7.8
	Related	40	45.5	34.8	56.4	47	49.5	39.1	59.9	37	41.1	30.8	52.0
VOMITING	Total	12	13.6	7.2	22.6	15	15.8	9.1	24.7	6	6.7	2.5	13.9
	Grade 2*3	7	8.0	3.3	15.7	11	11.6	5.9	19.8	3	3.3	0.7	9.4
	Grade 3	1	1.1	0.0	6.2	6	6.3	2.4	13.2	2	2.2	0.3	7.8
	Related	9	10.2	4.8	18.5	13	13.7	7.5	22.3	3	3.3	0.7	9.4

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		**2**							
Group		**Pooled HRV groups**				**Placebo**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
N		**273**				**97**			
COUGH	**Total**	151	55.3	49.2	61.3	49	50.5	40.2	60.8
	Grade 2*3	34	12.5	8.8	17.0	13	13.4	7.3	21.8
	Grade 3	6	2.2	0.8	4.7	1	1.0	0.0	5.6
	Related	118	43.2	37.3	49.3	43	44.3	34.2	54.8
DIARRHEA	**Total**	21	7.7	4.8	11.5	13	13.4	7.3	21.8
	Grade 2*3	14	5.1	2.8	8.5	6	6.2	2.3	13.0
	Grade 3	5	1.8	0.6	4.2	2	2.1	0.3	7.3
	Related	13	4.8	2.6	8.0	9	9.3	4.3	16.9
IRRITABILITY	**Total**	199	72.9	67.2	78.1	74	76.3	66.6	84.3
	Grade 2*3	83	30.4	25.0	36.2	31	32.0	22.9	42.2
	Grade 3	11	4.0	2.0	7.1	7	7.2	3.0	14.3
	Related	176	64.5	58.5	70.1	64	66.0	55.7	75.3
LOSS OF APPETITE	**Total**	81	29.7	24.3	35.5	30	30.9	21.9	41.1
	Grade 2*3	25	9.2	6.0	13.2	9	9.3	4.3	16.9
	Grade 3	3	1.1	0.2	3.2	1	1.0	0.0	5.6
	Related	65	23.8	18.9	29.3	26	26.8	18.3	36.8
FEVER	**Total**	143	52.4	46.3	58.4	52	53.6	43.2	63.8
	Grade 2*3	58	21.2	16.5	26.6	24	24.7	16.5	34.5
	Grade 3	8	2.9	1.3	5.7	3	3.1	0.6	8.8
	Related	124	45.4	39.4	51.5	43	44.3	34.2	54.8
VOMITING	**Total**	33	12.1	8.5	16.6	13	13.4	7.3	21.8
	Grade 2*3	21	7.7	4.8	11.5	7	7.2	3.0	14.3
	Grade 3	9	3.3	1.5	6.2	4	4.1	1.1	10.2
	Related	25	9.2	6.0	13.2	8	8.2	3.6	15.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/dose											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		**189**				**196**				**192**			
COUGH	**Total**	99	52.4	45.0	59.7	102	52.0	44.8	59.2	104	54.2	46.8	61.4
	Grade 2*3	19	10.1	6.2	15.3	29	14.8	10.1	20.6	22	11.5	7.3	16.8
	Grade 3	5	2.6	0.9	6.1	4	2.0	0.6	5.1	4	2.1	0.6	5.2
	Related	79	41.8	34.7	49.2	83	42.3	35.3	49.6	80	41.7	34.6	49.0
DIARRHEA	**Total**	12	6.3	3.3	10.8	12	6.1	3.2	10.5	24	12.5	8.2	18.0
	Grade 2*3	8	4.2	1.8	8.2	7	3.6	1.4	7.2	20	10.4	6.5	15.6
	Grade 3	3	1.6	0.3	4.6	3	1.5	0.3	4.4	6	3.1	1.2	6.7
	Related	7	3.7	1.5	7.5	9	4.6	2.1	8.5	17	8.9	5.2	13.8
IRRITABILITY	**Total**	146	77.2	70.6	83.0	146	74.5	67.8	80.4	153	79.7	73.3	85.1
	Grade 2*3	51	27.0	20.8	33.9	64	32.7	26.1	39.7	68	35.4	28.7	42.6
	Grade 3	9	4.8	2.2	8.8	8	4.1	1.8	7.9	8	4.2	1.8	8.0
	Related	135	71.4	64.4	77.8	132	67.3	60.3	73.9	140	72.9	66.0	79.1
LOSS OF APPETITE	**Total**	66	34.9	28.1	42.2	70	35.7	29.0	42.9	68	35.4	28.7	42.6
	Grade 2*3	20	10.6	6.6	15.9	14	7.1	4.0	11.7	17	8.9	5.2	13.8
	Grade 3	2	1.1	0.1	3.8	3	1.5	0.3	4.4	0	0.0	0.0	1.9
	Related	56	29.6	23.2	36.7	56	28.6	22.4	35.4	58	30.2	23.8	37.2
FEVER	**Total**	109	57.7	50.3	64.8	113	57.7	50.4	64.7	110	57.3	50.0	64.4
	Grade 2*3	41	21.7	16.0	28.3	51	26.0	20.0	32.8	48	25.0	19.0	31.7
	Grade 3	4	2.1	0.6	5.3	7	3.6	1.4	7.2	5	2.6	0.9	6.0
	Related	101	53.4	46.1	60.7	99	50.5	43.3	57.7	94	49.0	41.7	56.3
VOMITING	**Total**	34	18.0	12.8	24.2	36	18.4	13.2	24.5	25	13.0	8.6	18.6
	Grade 2*3	19	10.1	6.2	15.3	26	13.3	8.9	18.8	14	7.3	4.0	11.9
	Grade 3	6	3.2	1.2	6.8	13	6.6	3.6	11.1	8	4.2	1.8	8.0
	Related	26	13.8	9.2	19.5	29	14.8	10.1	20.6	16	8.3	4.8	13.2

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/dose							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		577				198			
COUGH	Total	305	52.9	48.7	57.0	104	52.5	45.3	59.6
	Grade 2*3	70	12.1	9.6	15.1	25	12.6	8.3	18.1
	Grade 3	13	2.3	1.2	3.8	1	0.5	0.0	2.8
	Related	242	41.9	37.9	46.1	86	43.4	36.4	50.6
DIARRHEA	Total	48	8.3	6.2	10.9	25	12.6	8.3	18.1
	Grade 2*3	35	6.1	4.3	8.3	14	7.1	3.9	11.6
	Grade 3	12	2.1	1.1	3.6	4	2.0	0.6	5.1
	Related	33	5.7	4.0	7.9	19	9.6	5.9	14.6
IRRITABILITY	Total	445	77.1	73.5	80.5	159	80.3	74.1	85.6
	Grade 2*3	183	31.7	27.9	35.7	66	33.3	26.8	40.4
	Grade 3	25	4.3	2.8	6.3	10	5.1	2.4	9.1
	Related	407	70.5	66.6	74.2	142	71.7	64.9	77.9
LOSS OF APPETITE	Total	204	35.4	31.5	39.4	65	32.8	26.3	39.8
	Grade 2*3	51	8.8	6.7	11.5	16	8.1	4.7	12.8
	Grade 3	5	0.9	0.3	2.0	1	0.5	0.0	2.8
	Related	170	29.5	25.8	33.4	59	29.8	23.5	36.7
FEVER	Total	332	57.5	53.4	61.6	110	55.6	48.3	62.6
	Grade 2*3	140	24.3	20.8	28.0	47	23.7	18.0	30.3
	Grade 3	16	2.8	1.6	4.5	5	2.5	0.8	5.8
	Related	294	51.0	46.8	55.1	98	49.5	42.3	56.7
VOMITING	Total	95	16.5	13.5	19.7	32	16.2	11.3	22.0
	Grade 2*3	59	10.2	7.9	13.0	19	9.6	5.9	14.6
	Grade 3	27	4.7	3.1	6.7	8	4.0	1.8	7.8
	Related	71	12.3	9.7	15.3	25	12.6	8.3	18.1

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/subject											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		101				101				102			
COUGH	Total	76	75.2	65.7	83.3	72	71.3	61.4	79.9	75	73.5	63.9	81.8
	Grade 2*3	19	18.8	11.7	27.8	23	22.8	15.0	32.2	22	21.6	14.0	30.8
	Grade 3	5	5.0	1.6	11.2	3	3.0	0.6	8.4	4	3.9	1.1	9.7
	Related	60	59.4	49.2	69.1	62	61.4	51.2	70.9	64	62.7	52.6	72.1
DIARRHEA	Total	12	11.9	6.3	19.8	12	11.9	6.3	19.8	21	20.6	13.2	29.7
	Grade 2*3	8	7.9	3.5	15.0	7	6.9	2.8	13.8	17	16.7	10.0	25.3
	Grade 3	3	3.0	0.6	8.4	3	3.0	0.6	8.4	6	5.9	2.2	12.4
	Related	7	6.9	2.8	13.8	9	8.9	4.2	16.2	16	15.7	9.2	24.2
IRRITABILITY	Total	89	88.1	80.2	93.7	87	86.1	77.8	92.2	93	91.2	83.9	95.9
	Grade 2*3	38	37.6	28.2	47.8	48	47.5	37.5	57.7	50	49.0	39.0	59.1
	Grade 3	8	7.9	3.5	15.0	7	6.9	2.8	13.8	6	5.9	2.2	12.4
	Related	86	85.1	76.7	91.4	81	80.2	71.1	87.5	89	87.3	79.2	93.0
LOSS OF APPETITE	Total	51	50.5	40.4	60.6	55	54.5	44.2	64.4	50	49.0	39.0	59.1
	Grade 2*3	18	17.8	10.9	26.7	12	11.9	6.3	19.8	13	12.7	7.0	20.8
	Grade 3	2	2.0	0.2	7.0	3	3.0	0.6	8.4	0	0.0	0.0	3.6
	Related	44	43.6	33.7	53.8	46	45.5	35.6	55.8	44	43.1	33.4	53.3
FEVER	Total	73	72.3	62.5	80.7	80	79.2	70.0	86.6	76	74.5	64.9	82.6
	Grade 2*3	36	35.6	26.4	45.8	43	42.6	32.8	52.8	41	40.2	30.6	50.4
	Grade 3	4	4.0	1.1	9.8	7	6.9	2.8	13.8	4	3.9	1.1	9.7
	Related	70	69.3	59.3	78.1	71	70.3	60.4	79.0	67	65.7	55.6	74.8
VOMITING	Total	29	28.7	20.1	38.6	32	31.7	22.8	41.7	22	21.6	14.0	30.8
	Grade 2*3	16	15.8	9.3	24.4	25	24.8	16.7	34.3	13	12.7	7.0	20.8
	Grade 3	6	5.9	2.2	12.5	13	12.9	7.0	21.0	7	6.9	2.8	13.6
	Related	21	20.8	13.4	30.0	27	26.7	18.4	36.5	15	14.7	8.5	23.1

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/subject							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		304				101			
COUGH	Total	223	73.4	68.0	78.2	71	70.3	60.4	79.0
	Grade 2*3	64	21.1	16.6	26.1	21	20.8	13.4	30.0
	Grade 3	12	3.9	2.1	6.8	1	1.0	0.0	5.4
	Related	186	61.2	55.5	66.7	64	63.4	53.2	72.7
DIARRHEA	Total	45	14.8	11.0	19.3	23	22.8	15.0	32.2
	Grade 2*3	32	10.5	7.3	14.5	14	13.9	7.8	22.2
	Grade 3	12	3.9	2.1	6.8	4	4.0	1.1	9.8
	Related	32	10.5	7.3	14.5	17	16.8	10.1	25.6
IRRITABILITY	Total	269	88.5	84.4	91.8	93	92.1	85.0	96.5
	Grade 2*3	136	44.7	39.1	50.5	49	48.5	38.4	58.7
	Grade 3	21	6.9	4.3	10.4	8	7.9	3.5	15.0
	Related	256	84.2	79.6	88.1	85	84.2	75.6	90.7
LOSS OF APPETITE	Total	156	51.3	45.5	57.1	49	48.5	38.4	58.7
	Grade 2*3	43	14.1	10.4	18.6	14	13.9	7.8	22.2
	Grade 3	5	1.6	0.5	3.8	1	1.0	0.0	5.4
	Related	134	44.1	38.4	49.9	47	46.5	36.5	56.7
FEVER	Total	229	75.3	70.1	80.1	77	76.2	66.7	84.1
	Grade 2*3	120	39.5	33.9	45.2	37	36.6	27.3	46.8
	Grade 3	15	4.9	2.8	8.0	5	5.0	1.6	11.2
	Related	208	68.4	62.9	73.6	69	68.3	58.3	77.2
VOMITING	Total	83	27.3	22.4	32.7	26	25.7	17.6	35.4
	Grade 2*3	54	17.8	13.6	22.5	17	16.8	10.1	25.6
	Grade 3	26	8.6	5.7	12.3	8	7.9	3.5	15.0
	Related	63	20.7	16.3	25.7	21	20.8	13.4	30.0

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73: Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		1											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		243				243				244			
COUGH	Total	146	60.1	53.6	66.3	135	55.6	49.1	61.9	153	62.7	56.3	68.8
	Grade 2*3	104	42.8	36.5	49.3	94	38.7	32.5	45.1	102	41.8	35.5	48.3
	Grade 3	34	14.0	9.9	19.0	41	16.9	12.4	22.2	41	16.8	12.3	22.1
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5
DIARRHEA	Total	3	1.2	0.3	3.6	3	1.2	0.3	3.6	3	1.2	0.3	3.6
	Grade 2*3	2	0.8	0.1	2.9	3	1.2	0.3	3.6	3	1.2	0.3	3.6
	Grade 3	1	0.4	0.0	2.3	1	0.4	0.0	2.3	3	1.2	0.3	3.6
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5
IRRITABILITY	Total	134	55.1	48.7	61.5	143	58.8	52.4	65.1	138	56.6	50.1	62.9
	Grade 2*3	107	44.0	37.7	50.5	111	45.7	39.3	52.2	102	41.8	35.5	48.3
	Grade 3	43	17.7	13.1	23.1	43	17.7	13.1	23.1	48	19.7	14.9	25.2
	Related	1	0.4	0.0	2.3	0	0.0	0.0	1.5	0	0.0	0.0	1.5
LOSS OF APPETITE	Total	75	30.9	25.1	37.1	75	30.9	25.1	37.1	75	30.7	25.0	36.9
	Grade 2*3	18	7.4	4.4	11.5	25	10.3	6.8	14.8	35	14.3	10.2	19.4
	Grade 3	2	0.8	0.1	2.9	4	1.6	0.5	4.2	10	4.1	2.0	7.4
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5
FEVER	Total	119	49.0	42.5	55.4	136	56.0	49.5	62.3	126	51.6	45.2	58.1
	Grade 2*3	24	9.9	6.4	14.3	19	7.8	4.8	11.9	23	9.4	6.1	13.8
	Grade 3	1	0.4	0.0	2.3	2	0.8	0.1	2.9	1	0.4	0.0	2.3
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5
VOMITING	Total	20	8.2	5.1	12.4	32	13.2	9.2	18.1	25	10.2	6.7	14.8
	Grade 2*3	8	3.3	1.4	6.4	17	7.0	4.1	11.0	12	4.9	2.6	8.4
	Grade 3	2	0.8	0.1	2.9	9	3.7	1.7	6.9	6	2.5	0.9	5.3
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		1							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		730				242			
COUGH	Total	434	59.5	55.8	63.0	152	62.8	56.4	68.9
	Grade 2*3	300	41.1	37.5	44.8	109	45.0	38.7	51.5
	Grade 3	116	15.9	13.3	18.7	28	11.6	7.8	16.3
	Related	0	0.0	0.0	0.5	1	0.4	0.0	2.3
DIARRHEA	Total	9	1.2	0.6	2.3	5	2.1	0.7	4.8
	Grade 2*3	8	1.1	0.5	2.1	3	1.2	0.3	3.6
	Grade 3	5	0.7	0.2	1.6	2	0.8	0.1	3.0
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5
IRRITABILITY	Total	415	56.8	53.2	60.5	153	63.2	56.8	69.3
	Grade 2*3	320	43.8	40.2	47.5	122	50.4	43.9	56.9
	Grade 3	134	18.4	15.6	21.4	52	21.5	16.5	27.2
	Related	1	0.1	0.0	0.8	0	0.0	0.0	1.5
LOSS OF APPETITE	Total	225	30.8	27.5	34.3	86	35.5	29.5	41.9
	Grade 2*3	78	10.7	8.5	13.2	31	12.8	8.9	17.7
	Grade 3	16	2.2	1.3	3.5	6	2.5	0.9	5.3
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5
FEVER	Total	381	52.2	48.5	55.9	145	59.9	53.4	66.1
	Grade 2*3	66	9.0	7.1	11.4	32	13.2	9.2	18.2
	Grade 3	4	0.5	0.1	1.4	3	1.2	0.3	3.6
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5
VOMITING	Total	77	10.5	8.4	13.0	21	8.7	5.5	13.0
	Grade 2*3	37	5.1	3.6	6.9	10	4.1	2.0	7.5
	Grade 3	17	2.3	1.4	3.7	4	1.7	0.5	4.2
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		2											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		235				231				233			
COUGH	Total	140	59.6	53.0	65.9	138	59.7	53.1	66.1	151	64.8	58.3	70.9
	Grade 2*3	91	38.7	32.5	45.3	88	38.1	31.8	44.7	105	45.1	38.6	51.7
	Grade 3	35	14.9	10.6	20.1	32	13.9	9.7	19.0	41	17.6	12.9	23.1
	Related	0	0.0	0.0	1.6	1	0.4	0.0	2.4	0	0.0	0.0	1.6
DIARRHEA	Total	3	1.3	0.3	3.7	1	0.4	0.0	2.4	4	1.7	0.5	4.3
	Grade 2*3	3	1.3	0.3	3.7	1	0.4	0.0	2.4	4	1.7	0.5	4.3
	Grade 3	2	0.9	0.1	3.0	1	0.4	0.0	2.4	3	1.3	0.3	3.7
	Related	0	0.0	0.0	1.6	0	0.0	0.0	1.6	0	0.0	0.0	1.6
IRRITABILITY	Total	109	46.4	39.9	53.0	113	48.9	42.3	55.6	123	52.8	46.2	59.3
	Grade 2*3	75	31.9	26.0	38.3	78	33.8	27.7	40.3	94	40.3	34.0	46.9
	Grade 3	33	14.0	9.9	19.2	28	12.1	8.2	17.0	39	16.7	12.2	22.2
	Related	0	0.0	0.0	1.6	0	0.0	0.0	1.6	0	0.0	0.0	1.6
LOSS OF APPETITE	Total	68	28.9	23.2	35.2	75	32.5	26.5	38.9	75	32.2	26.2	38.6
	Grade 2*3	28	11.9	8.1	16.8	31	13.4	9.3	18.5	37	15.9	11.4	21.2
	Grade 3	9	3.8	1.8	7.1	9	3.9	1.8	7.3	1	0.4	0.0	2.4
	Related	0	0.0	0.0	1.6	0	0.0	0.0	1.6	0	0.0	0.0	1.6
FEVER	Total	117	49.8	43.2	56.4	129	55.8	49.2	62.4	119	51.1	44.5	57.7
	Grade 2*3	35	14.9	10.6	20.1	44	19.0	14.2	24.7	37	15.9	11.4	21.2
	Grade 3	1	0.4	0.0	2.3	2	0.9	0.1	3.1	5	2.1	0.7	4.9
	Related	0	0.0	0.0	1.6	1	0.4	0.0	2.4	0	0.0	0.0	1.6
VOMITING	Total	10	4.3	2.1	7.7	18	7.8	4.7	12.0	25	10.7	7.1	15.4
	Grade 2*3	6	2.6	0.9	5.5	8	3.5	1.5	6.7	17	7.3	4.3	11.4
	Grade 3	3	1.3	0.3	3.7	5	2.2	0.7	5.0	9	3.9	1.8	7.2
	Related	0	0.0	0.0	1.6	0	0.0	0.0	1.6	0	0.0	0.0	1.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		**2**							
Group		**Pooled HRV groups**				**Placebo**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
N		**699**				**234**			
COUGH	**Total**	429	61.4	57.7	65.0	144	61.5	55.0	67.8
	Grade 2*3	284	40.6	37.0	44.4	110	47.0	40.5	53.6
	Grade 3	108	15.5	12.9	18.3	32	13.7	9.5	18.8
	Related	1	0.1	0.0	0.8	0	0.0	0.0	1.6
DIARRHEA	**Total**	8	1.1	0.5	2.2	5	2.1	0.7	4.9
	Grade 2*3	8	1.1	0.5	2.2	5	2.1	0.7	4.9
	Grade 3	6	0.9	0.3	1.9	3	1.3	0.3	3.7
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.6
IRRITABILITY	**Total**	345	49.4	45.6	53.1	123	52.6	46.0	59.1
	Grade 2*3	247	35.3	31.8	39.0	87	37.2	31.0	43.7
	Grade 3	100	14.3	11.8	17.1	27	11.5	7.7	16.3
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.6
LOSS OF APPETITE	**Total**	218	31.2	27.8	34.8	73	31.2	25.3	37.6
	Grade 2*3	96	13.7	11.3	16.5	39	16.7	12.1	22.1
	Grade 3	19	2.7	1.6	4.2	10	4.3	2.1	7.7
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.6
FEVER	**Total**	365	52.2	48.4	56.0	135	57.7	51.1	64.1
	Grade 2*3	116	16.6	13.9	19.6	28	12.0	8.1	16.8
	Grade 3	8	1.1	0.5	2.2	1	0.4	0.0	2.4
	Related	1	0.1	0.0	0.8	0	0.0	0.0	1.6
VOMITING	**Total**	53	7.6	5.7	9.8	20	8.5	5.3	12.9
	Grade 2*3	31	4.4	3.0	6.2	11	4.7	2.4	8.3
	Grade 3	17	2.4	1.4	3.9	5	2.1	0.7	4.9
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/dose											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		478				474				477			
COUGH	Total	286	59.8	55.3	64.3	273	57.6	53.0	62.1	304	63.7	59.2	68.1
	Grade 2*3	195	40.8	36.4	45.4	182	38.4	34.0	42.9	207	43.4	38.9	48.0
	Grade 3	69	14.4	11.4	17.9	73	15.4	12.3	19.0	82	17.2	13.9	20.9
	Related	0	0.0	0.0	0.8	1	0.2	0.0	1.2	0	0.0	0.0	0.8
DIARRHEA	Total	6	1.3	0.5	2.7	4	0.8	0.2	2.1	7	1.5	0.6	3.0
	Grade 2*3	5	1.0	0.3	2.4	4	0.8	0.2	2.1	7	1.5	0.6	3.0
	Grade 3	3	0.6	0.1	1.8	2	0.4	0.1	1.5	6	1.3	0.5	2.7
	Related	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.8
IRRITABILITY	Total	243	50.8	46.3	55.4	256	54.0	49.4	58.6	261	54.7	50.1	59.2
	Grade 2*3	182	38.1	33.7	42.6	189	39.9	35.4	44.4	196	41.1	36.6	45.7
	Grade 3	76	15.9	12.7	19.5	71	15.0	11.9	18.5	87	18.2	14.9	22.0
	Related	1	0.2	0.0	1.2	0	0.0	0.0	0.8	0	0.0	0.0	0.8
LOSS OF APPETITE	Total	143	29.9	25.8	34.2	150	31.6	27.5	36.0	150	31.4	27.3	35.8
	Grade 2*3	46	9.6	7.1	12.6	56	11.8	9.0	15.1	72	15.1	12.0	18.6
	Grade 3	11	2.3	1.2	4.1	13	2.7	1.5	4.6	11	2.3	1.2	4.1
	Related	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.8
FEVER	Total	236	49.4	44.8	54.0	265	55.9	51.3	60.4	245	51.4	46.8	55.9
	Grade 2*3	59	12.3	9.5	15.6	63	13.3	10.4	16.7	60	12.6	9.7	15.9
	Grade 3	2	0.4	0.1	1.5	4	0.8	0.2	2.1	6	1.3	0.5	2.7
	Related	0	0.0	0.0	0.8	1	0.2	0.0	1.2	0	0.0	0.0	0.8
VOMITING	Total	30	6.3	4.3	8.8	50	10.5	7.9	13.7	50	10.5	7.9	13.6
	Grade 2*3	14	2.9	1.6	4.9	25	5.3	3.4	7.7	29	6.1	4.1	8.6
	Grade 3	5	1.0	0.3	2.4	14	3.0	1.6	4.9	15	3.1	1.8	5.1
	Related	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.8

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/dose							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		1429				476			
COUGH	Total	863	60.4	57.8	62.9	296	62.2	57.7	66.6
	Grade 2*3	584	40.9	38.3	43.5	219	46.0	41.5	50.6
	Grade 3	224	15.7	13.8	17.7	60	12.6	9.8	15.9
	Related	1	0.1	0.0	0.4	1	0.2	0.0	1.2
DIARRHEA	Total	17	1.2	0.7	1.9	10	2.1	1.0	3.8
	Grade 2*3	16	1.1	0.6	1.8	8	1.7	0.7	3.3
	Grade 3	11	0.8	0.4	1.4	5	1.1	0.3	2.4
	Related	0	0.0	0.0	0.3	0	0.0	0.0	0.8
IRRITABILITY	Total	760	53.2	50.6	55.8	276	58.0	53.4	62.5
	Grade 2*3	567	39.7	37.1	42.3	209	43.9	39.4	48.5
	Grade 3	234	16.4	14.5	18.4	79	16.6	13.4	20.2
	Related	1	0.1	0.0	0.4	0	0.0	0.0	0.8
LOSS OF APPETITE	Total	443	31.0	28.6	33.5	159	33.4	29.2	37.8
	Grade 2*3	174	12.2	10.5	14.0	70	14.7	11.6	18.2
	Grade 3	35	2.4	1.7	3.4	16	3.4	1.9	5.4
	Related	0	0.0	0.0	0.3	0	0.0	0.0	0.8
FEVER	Total	746	52.2	49.6	54.8	280	58.8	54.3	63.3
	Grade 2*3	182	12.7	11.1	14.6	60	12.6	9.8	15.9
	Grade 3	12	0.8	0.4	1.5	4	0.8	0.2	2.1
	Related	1	0.1	0.0	0.4	0	0.0	0.0	0.8
VOMITING	Total	130	9.1	7.7	10.7	41	8.6	6.3	11.5
	Grade 2*3	68	4.8	3.7	6.0	21	4.4	2.8	6.7
	Grade 3	34	2.4	1.7	3.3	9	1.9	0.9	3.6
	Related	0	0.0	0.0	0.3	0	0.0	0.0	0.8

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/subject											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		243				243				244			
COUGH	Total	186	76.5	70.7	81.7	181	74.5	68.5	79.8	187	76.6	70.8	81.8
	Grade 2*3	138	56.8	50.3	63.1	139	57.2	50.7	63.5	145	59.4	53.0	65.6
	Grade 3	62	25.5	20.2	31.5	64	26.3	20.9	32.3	67	27.5	22.0	33.5
	Related	0	0.0	0.0	1.5	1	0.4	0.0	2.3	0	0.0	0.0	1.5
DIARRHEA	Total	6	2.5	0.9	5.3	4	1.6	0.5	4.2	7	2.9	1.2	5.8
	Grade 2*3	5	2.1	0.7	4.7	4	1.6	0.5	4.2	7	2.9	1.2	5.8
	Grade 3	3	1.2	0.3	3.6	2	0.8	0.1	2.9	6	2.5	0.9	5.3
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5
IRRITABILITY	Total	159	65.4	59.1	71.4	172	70.8	64.6	76.4	167	68.4	62.2	74.2
	Grade 2*3	133	54.7	48.2	61.1	141	58.0	51.5	64.3	132	54.1	47.6	60.5
	Grade 3	61	25.1	19.8	31.0	60	24.7	19.4	30.6	64	26.2	20.8	32.2
	Related	1	0.4	0.0	2.3	0	0.0	0.0	1.5	0	0.0	0.0	1.5
LOSS OF APPETITE	Total	101	41.6	35.3	48.0	113	46.5	40.1	53.0	109	44.7	38.3	51.1
	Grade 2*3	40	16.5	12.0	21.7	49	20.2	15.3	25.8	61	25.0	19.7	30.9
	Grade 3	9	3.7	1.7	6.9	12	4.9	2.6	8.5	11	4.5	2.3	7.9
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5
FEVER	Total	166	68.3	62.1	74.1	181	74.5	68.5	79.8	167	68.4	62.2	74.2
	Grade 2*3	47	19.3	14.6	24.9	57	23.5	18.3	29.3	51	20.9	16.0	26.5
	Grade 3	2	0.8	0.1	2.9	4	1.6	0.5	4.2	6	2.5	0.9	5.3
	Related	0	0.0	0.0	1.5	1	0.4	0.0	2.3	0	0.0	0.0	1.5
VOMITING	Total	28	11.5	7.8	16.2	45	18.5	13.8	24.0	45	18.4	13.8	23.9
	Grade 2*3	12	4.9	2.6	8.5	23	9.5	6.1	13.9	26	10.7	7.1	15.2
	Grade 3	5	2.1	0.7	4.7	14	5.8	3.2	9.5	14	5.7	3.2	9.4
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/subject							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		730				242			
COUGH	Total	554	75.9	72.6	79.0	195	80.6	75.0	85.4
	Grade 2*3	422	57.8	54.1	61.4	160	66.1	59.8	72.1
	Grade 3	193	26.4	23.3	29.8	51	21.1	16.1	26.8
	Related	1	0.1	0.0	0.8	1	0.4	0.0	2.3
DIARRHEA	Total	17	2.3	1.4	3.7	9	3.7	1.7	6.9
	Grade 2*3	16	2.2	1.3	3.5	7	2.9	1.2	5.9
	Grade 3	11	1.5	0.8	2.7	4	1.7	0.5	4.2
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5
IRRITABILITY	Total	498	68.2	64.7	71.6	175	72.3	66.2	77.9
	Grade 2*3	406	55.6	51.9	59.3	146	60.3	53.9	66.5
	Grade 3	185	25.3	22.2	28.7	68	28.1	22.5	34.2
	Related	1	0.1	0.0	0.8	0	0.0	0.0	1.5
LOSS OF APPETITE	Total	323	44.2	40.6	47.9	115	47.5	41.1	54.0
	Grade 2*3	150	20.5	17.7	23.7	57	23.6	18.4	29.4
	Grade 3	32	4.4	3.0	6.1	16	6.6	3.8	10.5
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5
FEVER	Total	514	70.4	67.0	73.7	184	76.0	70.1	81.3
	Grade 2*3	155	21.2	18.3	24.4	54	22.3	17.2	28.1
	Grade 3	12	1.6	0.9	2.9	4	1.7	0.5	4.2
	Related	1	0.1	0.0	0.8	0	0.0	0.0	1.5
VOMITING	Total	118	16.2	13.6	19.0	38	15.7	11.4	20.9
	Grade 2*3	61	8.4	6.5	10.6	19	7.9	4.8	12.0
	Grade 3	33	4.5	3.1	6.3	9	3.7	1.7	6.9
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 74: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 194				HRV_5.2 N = 196				HRV_5.8 N = 194				Pooled HRV groups N = 584				Placebo N = 194			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		153	78.9	72.4	84.4	154	78.6	72.2	84.1	146	75.3	68.6	81.2	453	77.6	74	80.9	153	78.9	72.4	84.4
Application site (1820)	Injection site reaction (0058)	7	3.6	1.5	7.3	5	2.6	0.8	5.9	4	2.1	0.6	5.2	16	2.7	1.6	4.4	7	3.6	1.5	7.3
	Otitis externa (0059)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.8	1	0.2	0	1	0	0	0	1.9
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	1	0.5	0	2.8
	Allergic reaction (0712)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Allergy (1058)	3	1.5	0.3	4.5	12	6.1	3.2	10.5	5	2.6	0.8	5.9	20	3.4	2.1	5.2	9	4.6	2.1	8.6
	Fever (0725)	33	17	12	23.1	26	13.3	8.9	18.8	34	17.5	12.5	23.6	93	15.9	13	19.1	23	11.9	7.7	17.3
	Injury (9001)	2	1	0.1	3.7	0	0	0	1.9	0	0	0	1.9	2	0.3	0	1.2	0	0	0	1.9
	Pallor (0220)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Cardiovascular general (1010)	Cyanosis (0501)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
Fetal (1500)	Vascular malformation peripheral (0764)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 74 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 194				HRV_5.2 N = 196				HRV_5.8 N = 194				Pooled HRV groups N = 584				Placebo N = 194			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Gastrointestinal system (600)	Abdominal pain (0268)	1	0.5	0	2.8	1	0.5	0	2.8	1	0.5	0	2.8	3	0.5	0.1	1.5	1	0.5	0	2.8
	Anorexia (0165)	4	2.1	0.6	5.2	5	2.6	0.8	5.9	2	1	0.1	3.7	11	1.9	0.9	3.3	5	2.6	0.8	5.9
	Constipation (0204)	3	1.5	0.3	4.5	0	0	0	1.9	2	1	0.1	3.7	5	0.9	0.3	2	4	2.1	0.6	5.2
	Gastroenteritis (0293)	3	1.5	0.3	4.5	5	2.6	0.8	5.9	1	0.5	0	2.8	9	1.5	0.7	2.9	4	2.1	0.6	5.2
	Gastroesophageal reflux (1149)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Gastrointestinal disorder nos (1262)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.8	1	0.2	0	1	1	0.5	0	2.8
	Stomatitis (0327)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Vomiting (0228)	3	1.5	0.3	4.5	4	2	0.6	5.1	5	2.6	0.8	5.9	12	2.1	1.1	3.6	8	4.1	1.8	8
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Earache (0260)	2	1	0.1	3.7	1	0.5	0	2.8	1	0.5	0	2.8	4	0.7	0.2	1.7	2	1	0.1	3.7
Neoplasm (1700)	Neoplasm nos (1259)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
Psychiatric (500)	Nervousness (0188)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Red blood cell (1210)	Anemia (0544)	1	0.5	0	2.8	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
Reproductive female (1420)	Leukorrhea (0654)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.8	1	0.2	0	1	0	0	0	1.9

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 74 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 194				HRV_5.2 N = 196				HRV_5.8 N = 194				Pooled HRV groups N = 584				Placebo N = 194			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Resistance mechanism (1830)	Abscess (0887)	1	0.5	0	2.8	1	0.5	0	2.8	2	1	0.1	3.7	4	0.7	0.2	1.7	0	0	0	1.9
	Infection (0736)	10	5.2	2.5	9.3	8	4.1	1.8	7.9	10	5.2	2.5	9.3	28	4.8	3.2	6.9	15	7.7	4.4	12.4
	Infection bacterial (0738)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Infection viral (0740)	99	51	43.8	58.3	99	50.5	43.3	57.7	94	48.5	41.2	55.7	292	50	45.9	54.1	101	52.1	44.8	59.3
	Moniliasis (0741)	1	0.5	0	2.8	7	3.6	1.4	7.2	2	1	0.1	3.7	10	1.7	0.8	3.1	2	1	0.1	3.7
	Otitis media (0750)	0	0	0	1.9	6	3.1	1.1	6.5	2	1	0.1	3.7	8	1.4	0.6	2.7	2	1	0.1	3.7
	Upper resp tract infection (0543)	20	10.3	6.4	15.5	12	6.1	3.2	10.5	14	7.2	4	11.8	46	7.9	5.8	10.4	15	7.7	4.4	12.4
Respiratory system (1100)	Asthma (1367)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Bronchitis (0805)	12	6.2	3.2	10.6	14	7.1	4	11.7	10	5.2	2.5	9.3	36	6.2	4.4	8.4	4	2.1	0.6	5.2
	Bronchospasm (0511)	1	0.5	0	2.8	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Coughing (0513)	24	12.4	8.1	17.8	23	11.7	7.6	17.1	23	11.9	7.7	17.3	70	12	9.5	14.9	15	7.7	4.4	12.4
	Dyspnea (0514)	0	0	0	1.9	1	0.5	0	2.8	1	0.5	0	2.8	2	0.3	0	1.2	1	0.5	0	2.8
	Laryngitis (0521)	1	0.5	0	2.8	1	0.5	0	2.8	1	0.5	0	2.8	3	0.5	0.1	1.5	0	0	0	1.9
	Pharyngitis (0523)	3	1.5	0.3	4.5	8	4.1	1.8	7.9	4	2.1	0.6	5.2	15	2.6	1.4	4.2	4	2.1	0.6	5.2
Respiratory system (1100)	Pneumonia (0528)	4	2.1	0.6	5.2	4	2	0.6	5.1	4	2.1	0.6	5.2	12	2.1	1.1	3.6	3	1.5	0.3	4.5
	Respiratory disorder (0536)	0	0	0	1.9	6	3.1	1.1	6.5	1	0.5	0	2.8	7	1.2	0.5	2.5	2	1	0.1	3.7
	Rhinitis (0539)	8	4.1	1.8	8	15	7.7	4.3	12.3	11	5.7	2.9	9.9	34	5.8	4.1	8	14	7.2	4	11.8
	Sputum increased (0541)	3	1.5	0.3	4.5	8	4.1	1.8	7.9	2	1	0.1	3.7	13	2.2	1.2	3.8	3	1.5	0.3	4.5
Secondary term (2000)	Varicella (1516)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 74 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 194				HRV_5.2 N = 196				HRV_5.8 N = 194				Pooled HRV groups N = 584				Placebo N = 194			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Skin and appendages (100)	Alopecia (0002)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Dermatitis (0007)	1	0.5	0	2.8	3	1.5	0.3	4.4	2	1	0.1	3.7	6	1	0.4	2.2	0	0	0	1.9
	Furunculosis (0016)	3	1.5	0.3	4.5	1	0.5	0	2.8	1	0.5	0	2.8	5	0.9	0.3	2	0	0	0	1.9
	Pruritus (0024)	0	0	0	1.9	3	1.5	0.3	4.4	2	1	0.1	3.7	5	0.9	0.3	2	0	0	0	1.9
	Rash (0027)	1	0.5	0	2.8	1	0.5	0	2.8	0	0	0	1.9	2	0.3	0	1.2	0	0	0	1.9
	Rash erythematous (0028)	2	1	0.1	3.7	0	0	0	1.9	0	0	0	1.9	2	0.3	0	1.2	1	0.5	0	2.8
	Rash maculo-papular (0030)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Rash pustular (0032)	0	0	0	1.9	1	0.5	0	2.8	2	1	0.1	3.7	3	0.5	0.1	1.5	0	0	0	1.9
Skin and appendages (100)	Seborrhea (0033)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Skin disorder (0037)	6	3.1	1.1	6.6	8	4.1	1.8	7.9	9	4.6	2.1	8.6	23	3.9	2.5	5.9	10	5.2	2.5	9.3
	Sweat gland disorder(1166)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.8	1	0.2	0	1	0	0	0	1.9
Urinary system (1300)	Dysuria (0601)	0	0	0	1.9	1	0.5	0	2.8	2	1	0.1	3.7	3	0.5	0.1	1.5	0	0	0	1.9
Vision (431)	Blepharitis (1007)	1	0.5	0	2.8	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Conjunctivitis (0238)	3	1.5	0.3	4.5	4	2	0.6	5.1	3	1.5	0.3	4.5	10	1.7	0.8	3.1	3	1.5	0.3	4.5
White cell and reticuloendothelial system (1220)	Lymphadenopathy cervical (0578)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.8	1	0.2	0	1	0	0	0	1.9

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 75: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 101				HRV_5.2 N = 101				HRV_5.8 N = 102				Pooled HRV groups N = 304				Placebo N = 101			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		82	81.2	72.2	88.3	90	89.1	81.3	94.4	87	85.3	76.9	91.5	259	85.2	80.7	89	87	86.1	77.8	92.2
Application site (1820)	Dermatitis contact (0049)	4	4	1.1	9.8	7	6.9	2.8	13.8	4	3.9	1.1	9.7	15	4.9	2.8	8	5	5	1.6	11.2
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	3.6	1	1	0	5.4	1	1	0	5.3	2	0.7	0.1	2.4	0	0	0	3.6
	Death, nos (0722)	0	0	0	3.6	0	0	0	3.6	1	1	0	5.3	1	0.3	0	1.8	0	0	0	3.6
	Edema generalised (0400)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Fever (0725)	11	10.9	5.6	18.7	18	17.8	10.9	26.7	11	10.8	5.5	18.5	40	13.2	9.6	17.5	18	17.8	10.9	26.7
	Injury (9001)	1	1	0	5.4	0	0	0	3.6	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Fever convulsions (1357)	0	0	0	3.6	0	0	0	3.6	1	1	0	5.3	1	0.3	0	1.8	0	0	0	3.6
Gastrointestinal system (600)	Abdominal pain (0268)	28	27.7	19.3	37.5	25	24.8	16.7	34.3	22	21.6	14	30.8	75	24.7	19.9	29.9	22	21.8	14.2	31.1
	Anorexia (0165)	17	16.8	10.1	25.6	16	15.8	9.3	24.4	12	11.8	6.2	19.6	45	14.8	11	19.3	21	20.8	13.4	30
	Constipation (0204)	8	7.9	3.5	15	10	9.9	4.9	17.5	8	7.8	3.4	14.9	26	8.6	5.7	12.3	2	2	0.2	7
	Gastroesophageal reflux (1149)	4	4	1.1	9.8	6	5.9	2.2	12.5	7	6.9	2.8	13.6	17	5.6	3.3	8.8	3	3	0.6	8.4
	Vomiting (0228)	11	10.9	5.6	18.7	13	12.9	7	21	11	10.8	5.5	18.5	35	11.5	8.2	15.6	12	11.9	6.3	19.8
Psychiatric (500)	Nervousness (0188)	30	29.7	21	39.6	26	25.7	17.6	35.4	30	29.4	20.8	39.3	86	28.3	23.3	33.7	33	32.7	23.7	42.7

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 75 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 101				HRV_5.2 N = 101				HRV_5.8 N = 102				Pooled HRV groups N = 304				Placebo N = 101			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Resistance mechanism (1830)	Infection bacterial (0738)	0	0	0	3.6	1	1	0	5.4	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
	Infection viral (0740)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Moniliasis (0741)	5	5	1.6	11.2	5	5	1.6	11.2	1	1	0	5.3	11	3.6	1.8	6.4	3	3	0.6	8.4
	Otitis media (0750)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Upper resp tract infection (0543)	21	20.8	13.4	30	24	23.8	15.9	33.3	30	29.4	20.8	39.3	75	24.7	19.9	29.9	25	24.8	16.7	34.3
Respiratory system (1100)	Bronchitis (0805)	1	1	0	5.4	1	1	0	5.4	0	0	0	3.6	2	0.7	0.1	2.4	0	0	0	3.6
	Coughing (0513)	6	5.9	2.2	12.5	2	2	0.2	7	6	5.9	2.2	12.4	14	4.6	2.5	7.6	5	5	1.6	11.2
	Laryngitis (0521)	0	0	0	3.6	1	1	0	5.4	1	1	0	5.3	2	0.7	0.1	2.4	2	2	0.2	7
	Pharyngitis (0523)	52	51.5	41.3	61.6	64	63.4	53.2	72.7	59	57.8	47.7	67.6	175	57.6	51.8	63.2	62	61.4	51.2	70.9
	Pneumonia (0528)	4	4	1.1	9.8	10	9.9	4.9	17.5	4	3.9	1.1	9.7	18	5.9	3.5	9.2	8	7.9	3.5	15
Secondary term (2000)	Varicella (1516)	1	1	0	5.4	0	0	0	3.6	0	0	0	3.6	1	0.3	0	1.8	4	4	1.1	9.8
Skin and appendages (100)	Dermatitis (0007)	1	1	0	5.4	1	1	0	5.4	2	2	0.2	6.9	4	1.3	0.4	3.3	0	0	0	3.6
	Photosensitivity reaction (0022)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Rash erythematous (0028)	0	0	0	3.6	1	1	0	5.4	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
	Rash maculo-papular (0030)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Sweat gland disorder (1166)	1	1	0	5.4	1	1	0	5.4	1	1	0	5.3	3	1	0.2	2.9	0	0	0	3.6

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 75 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 101				HRV_5.2 N = 101				HRV_5.8 N = 102				Pooled HRV groups N = 304				Placebo N = 101			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Urinary system (1300)	Urinary tract infection (0628)	0	0	0	3.6	0	0	0	3.6	2	2	0.2	6.9	2	0.7	0.1	2.4	0	0	0	3.6
Vision (431)	Blepharitis (1007)	0	0	0	3.6	0	0	0	3.6	1	1	0	5.3	1	0.3	0	1.8	0	0	0	3.6
	Conjunctivitis (0238)	4	4	1.1	9.8	5	5	1.6	11.2	6	5.9	2.2	12.4	15	4.9	2.8	8	4	4	1.1	9.8

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 76: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 243				HRV_5.2 N = 243				HRV_5.8 N = 244				Pooled HRV groups N = 730				Placebo N = 242			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		115	47.3	40.9	53.8	110	45.3	38.9	51.8	95	38.9	32.8	45.4	320	43.8	40.2	47.5	102	42.1	35.9	48.6
Application site (1820)	Dermatitis contact (0049)	0	0	0	1.5	1	0.4	0	2.3	0	0	0	1.5	1	0.1	0	0.8	1	0.4	0	2.3
	Injection site reaction (0058)	0	0	0	1.5	0	0	0	1.5	1	0.4	0	2.3	1	0.1	0	0.8	0	0	0	1.5
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	2	0.8	0.1	3
	Allergy (1058)	0	0	0	1.5	0	0	0	1.5	1	0.4	0	2.3	1	0.1	0	0.8	0	0	0	1.5
	Injury (9001)	2	0.8	0.1	2.9	0	0	0	1.5	0	0	0	1.5	2	0.3	0	1	0	0	0	1.5
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	1.5	1	0.4	0	2.3	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Fever convulsions (1357)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Spasm generalized (0149)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	1	0.4	0	2.3
Gastrointestinal system (600)	Abdominal pain (0268)	4	1.6	0.5	4.2	4	1.6	0.5	4.2	2	0.8	0.1	2.9	10	1.4	0.7	2.5	2	0.8	0.1	3
	Anus disorder (0269)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Constipation (0204)	0	0	0	1.5	1	0.4	0	2.3	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Stomatitis (0327)	0	0	0	1.5	1	0.4	0	2.3	1	0.4	0	2.3	2	0.3	0	1	0	0	0	1.5
	Stomatitis aphthous (0751)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	1	0.4	0	2.3
Resistance mechanism (1830)	Abscess (0887)	0	0	0	1.5	1	0.4	0	2.3	1	0.4	0	2.3	2	0.3	0	1	0	0	0	1.5
	Infection (0736)	16	6.6	3.8	10.5	14	5.8	3.2	9.5	8	3.3	1.4	6.4	38	5.2	3.7	7.1	9	3.7	1.7	6.9
	Infection bacterial (0738)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	1	0.4	0	2.3
	Infection viral (0740)	72	29.6	24	35.8	61	25.1	19.8	31	61	25	19.7	30.9	194	26.6	23.4	29.9	69	28.5	22.9	34.6
	Moniliasis (0741)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Otitis media (0750)	5	2.1	0.7	4.7	5	2.1	0.7	4.7	1	0.4	0	2.3	11	1.5	0.8	2.7	8	3.3	1.4	6.4

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 76 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 243				HRV_5.2 N = 243				HRV_5.8 N = 244				Pooled HRV groups N = 730				Placebo N = 242			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Respiratory system (1100)	Atelectasis (1197)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	1	0.4	0	2.3
	Bronchitis (0805)	8	3.3	1.4	6.4	15	6.2	3.5	10	11	4.5	2.3	7.9	34	4.7	3.2	6.4	10	4.1	2	7.5
	Bronchospasm (0511)	13	5.3	2.9	9	9	3.7	1.7	6.9	12	4.9	2.6	8.4	34	4.7	3.2	6.4	7	2.9	1.2	5.9
	Laryngitis (0521)	0	0	0	1.5	1	0.4	0	2.3	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Pharyngitis (0523)	4	1.6	0.5	4.2	2	0.8	0.1	2.9	1	0.4	0	2.3	7	1	0.4	2	4	1.7	0.5	4.2
	Pneumonia (0528)	6	2.5	0.9	5.3	11	4.5	2.3	8	12	4.9	2.6	8.4	29	4	2.7	5.7	9	3.7	1.7	6.9
	Rhinitis (0539)	1	0.4	0	2.3	0	0	0	1.5	1	0.4	0	2.3	2	0.3	0	1	0	0	0	1.5
Secondary term (2000)	Varicella (1516)	1	0.4	0	2.3	0	0	0	1.5	1	0.4	0	2.3	2	0.3	0	1	0	0	0	1.5
Skin and appendages (100)	Dermatitis (0007)	0	0	0	1.5	0	0	0	1.5	1	0.4	0	2.3	1	0.1	0	0.8	0	0	0	1.5
	Dermatitis fungal (0009)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Rash pustular (0032)	0	0	0	1.5	1	0.4	0	2.3	1	0.4	0	2.3	2	0.3	0	1	2	0.8	0.1	3
Urinary system (1300)	Urinary tract infection (0628)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	2	0.8	0.1	3
Vision (431)	Conjunctivitis (0238)	6	2.5	0.9	5.3	4	1.6	0.5	4.2	0	0	0	1.5	10	1.4	0.7	2.5	3	1.2	0.3	3.6

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 77: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 381				HRV_5.2 D = 379				HRV_5.8 D = 386				Pooled HRV groups D = 1146				Placebo D = 385			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		217	57	51.8	62	220	58	52.9	63.1	201	52.1	47	57.2	638	55.7	52.7	58.6	216	56.1	51	61.1
Application site (1820)	Injection site reaction (0058)	7	1.8	0.7	3.7	5	1.3	0.4	3.1	4	1	0.3	2.6	16	1.4	0.8	2.3	8	2.1	0.9	4.1
	Otitis externa (0059)	0	0	0	1	0	0	0	1	1	0.3	0	1.4	1	0.1	0	0.5	0	0	0	1
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	1	0.3	0	1.4
	Allergic reaction (0712)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
	Allergy (1058)	3	0.8	0.2	2.3	14	3.7	2	6.1	5	1.3	0.4	3	22	1.9	1.2	2.9	9	2.3	1.1	4.4
	Fever (0725)	34	8.9	6.3	12.2	27	7.1	4.7	10.2	36	9.3	6.6	12.7	97	8.5	6.9	10.2	24	6.2	4	9.1
	Injury (9001)	2	0.5	0.1	1.9	0	0	0	1	0	0	0	1	2	0.2	0	0.6	0	0	0	1
	Pallor (0220)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Cardiovascular general (1010)	Cyanosis (0501)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
Fetal (1500)	Vascular malformation peripheral (0764)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 77 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 381				HRV_5.2 D = 379				HRV_5.8 D = 386				Pooled HRV groups D = 1146				Placebo D = 385			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Gastrointestinal system (600)	Abdominal pain (0268)	1	0.3	0	1.5	1	0.3	0	1.5	1	0.3	0	1.4	3	0.3	0.1	0.8	1	0.3	0	1.4
	Anorexia (0165)	4	1	0.3	2.7	5	1.3	0.4	3.1	2	0.5	0.1	1.9	11	1	0.5	1.7	5	1.3	0.4	3
	Constipation (0204)	3	0.8	0.2	2.3	0	0	0	1	2	0.5	0.1	1.9	5	0.4	0.1	1	4	1	0.3	2.6
	Gastroenteritis (0293)	3	0.8	0.2	2.3	5	1.3	0.4	3.1	1	0.3	0	1.4	9	0.8	0.4	1.5	4	1	0.3	2.6
	Gastroesophageal reflux (1149)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Gastrointestinal disorder nos (1262)	0	0	0	1	0	0	0	1	1	0.3	0	1.4	1	0.1	0	0.5	1	0.3	0	1.4
	Stomatitis (0327)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
	Vomiting (0228)	3	0.8	0.2	2.3	4	1.1	0.3	2.7	5	1.3	0.4	3	12	1	0.5	1.8	8	2.1	0.9	4.1
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Earache (0260)	2	0.5	0.1	1.9	1	0.3	0	1.5	1	0.3	0	1.4	4	0.3	0.1	0.9	2	0.5	0.1	1.9
Neoplasm (1700)	Neoplasm nos (1259)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
Psychiatric (500)	Nervousness (0188)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Red blood cell (1210)	Anemia (0544)	1	0.3	0	1.5	0	0	0	1	0	0	0	1	1	0.1	0	0.5	0	0	0	1
Reproductive female (1420)	Leukorrhea (0654)	0	0	0	1	0	0	0	1	1	0.3	0	1.4	1	0.1	0	0.5	0	0	0	1

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 77 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 381				HRV_5.2 D = 379				HRV_5.8 D = 386				Pooled HRV groups D = 1146				Placebo D = 385			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Resistance mechanism (1830)	Abscess (0887)	1	0.3	0	1.5	1	0.3	0	1.5	2	0.5	0.1	1.9	4	0.3	0.1	0.9	0	0	0	1
	Infection (0736)	10	2.6	1.3	4.8	9	2.4	1.1	4.5	10	2.6	1.2	4.7	29	2.5	1.7	3.6	15	3.9	2.2	6.3
	Infection bacterial (0738)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Infection viral (0740)	113	29.7	25.1	34.5	115	30.3	25.8	35.2	114	29.5	25	34.4	342	29.8	27.2	32.6	127	33	28.3	37.9
	Moniliasis (0741)	1	0.3	0	1.5	7	1.8	0.7	3.8	2	0.5	0.1	1.9	10	0.9	0.4	1.6	2	0.5	0.1	1.9
	Otitis media (0750)	0	0	0	1	6	1.6	0.6	3.4	2	0.5	0.1	1.9	8	0.7	0.3	1.4	2	0.5	0.1	1.9
	Upper resp tract infection (0543)	21	5.5	3.4	8.3	12	3.2	1.6	5.5	16	4.1	2.4	6.6	49	4.3	3.2	5.6	16	4.2	2.4	6.7
Respiratory system (1100)	Asthma (1367)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Bronchitis (0805)	12	3.1	1.6	5.4	14	3.7	2	6.1	10	2.6	1.2	4.7	36	3.1	2.2	4.3	4	1	0.3	2.6
	Bronchospasm (0511)	1	0.3	0	1.5	0	0	0	1	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Coughing (0513)	27	7.1	4.7	10.1	23	6.1	3.9	9	25	6.5	4.2	9.4	75	6.5	5.2	8.1	16	4.2	2.4	6.7
	Dyspnea (0514)	0	0	0	1	1	0.3	0	1.5	1	0.3	0	1.4	2	0.2	0	0.6	1	0.3	0	1.4
	Laryngitis (0521)	1	0.3	0	1.5	1	0.3	0	1.5	1	0.3	0	1.4	3	0.3	0.1	0.8	0	0	0	1
	Pharyngitis (0523)	3	0.8	0.2	2.3	9	2.4	1.1	4.5	4	1	0.3	2.6	16	1.4	0.8	2.3	4	1	0.3	2.6
	Pneumonia (0528)	4	1	0.3	2.7	4	1.1	0.3	2.7	4	1	0.3	2.6	12	1	0.5	1.8	3	0.8	0.2	2.3
	Respiratory disorder (0536)	0	0	0	1	7	1.8	0.7	3.8	1	0.3	0	1.4	8	0.7	0.3	1.4	2	0.5	0.1	1.9
	Rhinitis (0539)	8	2.1	0.9	4.1	15	4	2.2	6.4	12	3.1	1.6	5.4	35	3.1	2.1	4.2	14	3.6	2	6
	Sputum increased (0541)	3	0.8	0.2	2.3	9	2.4	1.1	4.5	2	0.5	0.1	1.9	14	1.2	0.7	2	3	0.8	0.2	2.3
Secondary term (2000)	Varicella (1516)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 77 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 381				HRV_5.2 D = 379				HRV_5.8 D = 386				Pooled HRV groups D = 1146				Placebo D = 385			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Skin and appendages (100)	Alopecia (0002)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Dermatitis (0007)	1	0.3	0	1.5	3	0.8	0.2	2.3	2	0.5	0.1	1.9	6	0.5	0.2	1.1	0	0	0	1
	Furunculosis (0016)	3	0.8	0.2	2.3	1	0.3	0	1.5	1	0.3	0	1.4	5	0.4	0.1	1	0	0	0	1
	Pruritus (0024)	0	0	0	1	3	0.8	0.2	2.3	2	0.5	0.1	1.9	5	0.4	0.1	1	0	0	0	1
	Rash (0027)	1	0.3	0	1.5	1	0.3	0	1.5	0	0	0	1	2	0.2	0	0.6	0	0	0	1
	Rash erythematous (0028)	2	0.5	0.1	1.9	0	0	0	1	0	0	0	1	2	0.2	0	0.6	1	0.3	0	1.4
	Rash maculo-papular (0030)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Rash pustular (0032)	0	0	0	1	1	0.3	0	1.5	2	0.5	0.1	1.9	3	0.3	0.1	0.8	0	0	0	1
	Seborrhea (0033)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Skin disorder (0037)	6	1.6	0.6	3.4	8	2.1	0.9	4.1	10	2.6	1.2	4.7	24	2.1	1.3	3.1	10	2.6	1.3	4.7
	Sweat gland disorder (1166)	0	0	0	1	0	0	0	1	1	0.3	0	1.4	1	0.1	0	0.5	0	0	0	1
Urinary system (1300)	Dysuria (0601)	0	0	0	1	1	0.3	0	1.5	2	0.5	0.1	1.9	3	0.3	0.1	0.8	0	0	0	1
Vision (431)	Blepharitis (1007)	1	0.3	0	1.5	0	0	0	1	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Conjunctivitis (0238)	3	0.8	0.2	2.3	4	1.1	0.3	2.7	3	0.8	0.2	2.3	10	0.9	0.4	1.6	3	0.8	0.2	2.3
White cell and reticuloendothelial system (1220)	Lymphadenopathy cervical (0578)	0	0	0	1	0	0	0	1	1	0.3	0	1.4	1	0.1	0	0.5	0	0	0	1

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 78: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 189				HRV_5.2 D = 196				HRV_5.8 D = 192				Pooled HRV groups D = 577				Placebo D = 198			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		131	69.3	62.2	75.8	147	75	68.3	80.9	144	75	68.3	81	422	73.1	69.3	76.7	139	70.2	63.3	76.5
Application site (1820)	Dermatitis contact (0049)	4	2.1	0.6	5.3	7	3.6	1.4	7.2	4	2.1	0.6	5.2	15	2.6	1.5	4.3	6	3	1.1	6.5
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	1.9	1	0.5	0	2.8	1	0.5	0	2.9	2	0.3	0	1.2	0	0	0	1.8
	Death, nos (0722)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.9	1	0.2	0	1	0	0	0	1.8
	Edema generalised (0400)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Fever (0725)	11	5.8	2.9	10.2	19	9.7	5.9	14.7	11	5.7	2.9	10	41	7.1	5.1	9.5	19	9.6	5.9	14.6
	Injury (9001)	1	0.5	0	2.9	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Fever convulsions (1357)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.9	1	0.2	0	1	0	0	0	1.8
Gastrointestinal system (600)	Abdominal pain (0268)	30	15.9	11	21.9	26	13.3	8.9	18.8	27	14.1	9.5	19.8	83	14.4	11.6	17.5	22	11.1	7.1	16.3
	Anorexia (0165)	20	10.6	6.6	15.9	18	9.2	5.5	14.1	13	6.8	3.7	11.3	51	8.8	6.7	11.5	22	11.1	7.1	16.3
	Constipation (0204)	8	4.2	1.8	8.2	11	5.6	2.8	9.8	9	4.7	2.2	8.7	28	4.9	3.2	6.9	2	1	0.1	3.6
	Gastroesophageal reflux (1149)	4	2.1	0.6	5.3	6	3.1	1.1	6.5	7	3.6	1.5	7.4	17	2.9	1.7	4.7	3	1.5	0.3	4.4
	Vomiting (0228)	11	5.8	2.9	10.2	14	7.1	4	11.7	12	6.3	3.3	10.7	37	6.4	4.6	8.7	12	6.1	3.2	10.3
Psychiatric (500)	Nervousness (0188)	39	20.6	15.1	27.1	30	15.3	10.6	21.1	35	18.2	13	24.4	104	18	15	21.4	36	18.2	13.1	24.3
Resistance mechanism (1830)	Infection bacterial (0738)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
	Infection viral (0740)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Moniliasis (0741)	5	2.6	0.9	6.1	5	2.6	0.8	5.9	1	0.5	0	2.9	11	1.9	1	3.4	3	1.5	0.3	4.4
	Otitis media (0750)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Upper resp tract infection (0543)	26	13.8	9.2	19.5	26	13.3	8.9	18.8	33	17.2	12.1	23.3	85	14.7	11.9	17.9	26	13.1	8.8	18.6

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 78 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 189				HRV_5.2 D = 196				HRV_5.8 D = 192				Pooled HRV groups D = 577				Placebo D = 198			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Respiratory system (1100)	Bronchitis (0805)	1	0.5	0	2.9	1	0.5	0	2.8	0	0	0	1.9	2	0.3	0	1.2	0	0	0	1.8
	Coughing (0513)	7	3.7	1.5	7.5	2	1	0.1	3.6	6	3.1	1.2	6.7	15	2.6	1.5	4.3	5	2.5	0.8	5.8
	Laryngitis (0521)	0	0	0	1.9	1	0.5	0	2.8	1	0.5	0	2.9	2	0.3	0	1.2	2	1	0.1	3.6
	Pharyngitis (0523)	68	36	29.1	43.3	89	45.4	38.3	52.7	77	40.1	33.1	47.4	234	40.6	36.5	44.7	77	38.9	32.1	46.1
	Pneumonia (0528)	4	2.1	0.6	5.3	10	5.1	2.5	9.2	4	2.1	0.6	5.2	18	3.1	1.9	4.9	8	4	1.8	7.8
Secondary term (2000)	Varicella (1516)	1	0.5	0	2.9	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	4	2	0.6	5.1
Skin and appendages (100)	Dermatitis (0007)	1	0.5	0	2.9	1	0.5	0	2.8	2	1	0.1	3.7	4	0.7	0.2	1.8	0	0	0	1.8
	Photosensitivity reaction (0022)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Rash erythematous (0028)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
	Rash maculo-papular (0030)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Sweat gland disorder (1166)	1	0.5	0	2.9	1	0.5	0	2.8	1	0.5	0	2.9	3	0.5	0.1	1.5	0	0	0	1.8
Urinary system (1300)	Urinary tract infection (0628)	0	0	0	1.9	0	0	0	1.9	2	1	0.1	3.7	2	0.3	0	1.2	0	0	0	1.8
Vision (431)	Blepharitis (1007)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.9	1	0.2	0	1	0	0	0	1.8
	Conjunctivitis (0238)	4	2.1	0.6	5.3	5	2.6	0.8	5.9	6	3.1	1.2	6.7	15	2.6	1.5	4.3	4	2	0.6	5.1

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 79: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 478				HRV_5.2 D = 474				HRV_5.8 D = 477				Pooled HRV groups D = 1429				Placebo D = 476			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		134	28	24	32.3	128	27	23.1	31.2	115	24.1	20.3	28.2	377	26.4	24.1	28.7	120	25.2	21.4	29.4
Application site (1820)	Dermatitis contact (0049)	0	0	0	0.8	1	0.2	0	1.2	0	0	0	0.8	1	0.1	0	0.4	1	0.2	0	1.2
	Injection site reaction (0058)	0	0	0	0.8	0	0	0	0.8	1	0.2	0	1.2	1	0.1	0	0.4	0	0	0	0.8
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	2	0.4	0.1	1.5
	Allergy (1058)	0	0	0	0.8	0	0	0	0.8	1	0.2	0	1.2	1	0.1	0	0.4	0	0	0	0.8
	Injury (9001)	2	0.4	0.1	1.5	0	0	0	0.8	0	0	0	0.8	2	0.1	0	0.5	0	0	0	0.8
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	0.8	1	0.2	0	1.2	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Fever convulsions (1357)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Spasm generalized (0149)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	1	0.2	0	1.2
Gastrointestinal system (600)	Abdominal pain (0268)	4	0.8	0.2	2.1	4	0.8	0.2	2.1	2	0.4	0.1	1.5	10	0.7	0.3	1.3	2	0.4	0.1	1.5
	Anus disorder (0269)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Constipation (0204)	0	0	0	0.8	1	0.2	0	1.2	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Stomatitis (0327)	0	0	0	0.8	1	0.2	0	1.2	1	0.2	0	1.2	2	0.1	0	0.5	0	0	0	0.8
	Stomatitis aphthous (0751)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	1	0.2	0	1.2

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 79 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 478				HRV_5.2 D = 474				HRV_5.8 D = 477				Pooled HRV groups D = 1429				Placebo D = 476			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Resistance mechanism (1830)	Abscess (0887)	0	0	0	0.8	1	0.2	0	1.2	1	0.2	0	1.2	2	0.1	0	0.5	0	0	0	0.8
	Infection (0736)	17	3.6	2.1	5.6	14	3	1.6	4.9	8	1.7	0.7	3.3	39	2.7	1.9	3.7	9	1.9	0.9	3.6
	Infection bacterial (0738)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	1	0.2	0	1.2
	Infection viral (0740)	81	16.9	13.7	20.6	70	14.8	11.7	18.3	71	14.9	11.8	18.4	222	15.5	13.7	17.5	77	16.2	13	19.8
	Moniliasis (0741)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Otitis media (0750)	5	1	0.3	2.4	5	1.1	0.3	2.4	1	0.2	0	1.2	11	0.8	0.4	1.4	8	1.7	0.7	3.3
Respiratory system (1100)	Atelectasis (1197)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	1	0.2	0	1.2
	Bronchitis (0805)	8	1.7	0.7	3.3	15	3.2	1.8	5.2	11	2.3	1.2	4.1	34	2.4	1.7	3.3	10	2.1	1	3.8
	Bronchospasm (0511)	13	2.7	1.5	4.6	9	1.9	0.9	3.6	12	2.5	1.3	4.4	34	2.4	1.7	3.3	8	1.7	0.7	3.3
	Laryngitis (0521)	0	0	0	0.8	1	0.2	0	1.2	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Pharyngitis (0523)	4	0.8	0.2	2.1	2	0.4	0.1	1.5	1	0.2	0	1.2	7	0.5	0.2	1	4	0.8	0.2	2.1
	Pneumonia (0528)	6	1.3	0.5	2.7	11	2.3	1.2	4.1	13	2.7	1.5	4.6	30	2.1	1.4	3	9	1.9	0.9	3.6
	Rhinitis (0539)	1	0.2	0	1.2	0	0	0	0.8	1	0.2	0	1.2	2	0.1	0	0.5	0	0	0	0.8
Secondary term (2000)	Varicella (1516)	1	0.2	0	1.2	0	0	0	0.8	1	0.2	0	1.2	2	0.1	0	0.5	0	0	0	0.8
Skin and appendages (100)	Dermatitis (0007)	0	0	0	0.8	0	0	0	0.8	1	0.2	0	1.2	1	0.1	0	0.4	0	0	0	0.8
	Dermatitis fungal (0009)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Rash pustular (0032)	0	0	0	0.8	1	0.2	0	1.2	1	0.2	0	1.2	2	0.1	0	0.5	2	0.4	0.1	1.5
Urinary system (1300)	Urinary tract infection (0628)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	3	0.6	0.1	1.8
Vision (431)	Conjunctivitis (0238)	6	1.3	0.5	2.7	4	0.8	0.2	2.1	0	0	0	0.8	10	0.7	0.3	1.3	3	0.6	0.1	1.8

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 80: Percentage of subjects with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine y)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 194				HRV_5.2 N = 196				HRV_5.8 N = 194				Pooled HRV groups N = 584				Placebo N = 194			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		2	1	0.1	3.7	0	0	0	1.9	0	0	0	1.9	2	0.3	0	1.2	4	2.1	0.6	5.2
Application site (1820)	Injection site reaction (0058)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Fever (0725)	1	0.5	0	2.8	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Pallor (0220)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Respiratory system (1100)	Bronchitis (0805)	1	0.5	0	2.8	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 81: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 381				HRV_5.2 D = 379				HRV_5.8 D = 386				Pooled HRV groups D = 1146				Placebo D = 385			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		2	0.5	0.1	1.9	0	0	0	1	0	0	0	1	2	0.2	0	0.6	4	1	0.3	2.6
Application site (1820)	Injection site reaction (0058)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
	Fever (0725)	1	0.3	0	1.5	0	0	0	1	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Pallor (0220)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Respiratory system (1100)	Bronchitis (0805)	1	0.3	0	1.5	0	0	0	1	0	0	0	1	1	0.1	0	0.5	0	0	0	1

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 82: Percentage of subjects with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 194				HRV_5.2 N = 196				HRV_5.8 N = 194				Pooled HRV groups N = 584				Placebo N = 194			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		8	4.1	1.8	8	10	5.1	2.5	9.2	6	3.1	1.1	6.6	24	4.1	2.7	6.1	10	5.2	2.5	9.3
Body as a whole general (1810)	Pallor (0220)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Gastrointestinal system (600)	Gastroenteritis (0293)	3	1.5	0.3	4.5	5	2.6	0.8	5.9	1	0.5	0	2.8	9	1.5	0.7	2.9	4	2.1	0.6	5.2
	Gastrointestinal disorder nos (1262)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.8	1	0.2	0	1	1	0.5	0	2.8
Resistance mechanism (1830)	Infection (0736)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	1	0.5	0	2.8
Respiratory system (1100)	Asthma (1367)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Bronchitis (0805)	2	1	0.1	3.7	3	1.5	0.3	4.4	0	0	0	1.9	5	0.9	0.3	2	0	0	0	1.9
	Pneumonia (0528)	4	2.1	0.6	5.2	2	1	0.1	3.6	4	2.1	0.6	5.2	10	1.7	0.8	3.1	3	1.5	0.3	4.5

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 83: Percentage of subjects with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 101				HRV_5.2 N = 101				HRV_5.8 N = 102				Pooled HRV groups N = 304				Placebo N = 101			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		6	5.9	2.2	12.5	17	16.8	10.1	25.6	8	7.8	3.4	14.9	31	10.2	7	14.2	5	5	1.6	11.2
Application site (1820)	Dermatitis contact (0049)	0	0	0	3.6	1	1	0	5.4	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	3.6	1	1	0	5.4	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
	Death, nos (0722)	0	0	0	3.6	0	0	0	3.6	1	1	0	5.3	1	0.3	0	1.8	0	0	0	3.6
	Edema generalised (0400)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Fever (0725)	0	0	0	3.6	2	2	0.2	7	1	1	0	5.3	3	1	0.2	2.9	0	0	0	3.6
Central and peripheral nervous system (410)	Fever convulsions (1357)	0	0	0	3.6	0	0	0	3.6	1	1	0	5.3	1	0.3	0	1.8	0	0	0	3.6
Gastrointestinal system (600)	Abdominal pain (0268)	2	2	0.2	7	3	3	0.6	8.4	1	1	0	5.3	6	2	0.7	4.2	0	0	0	3.6
	Anorexia (0165)	1	1	0	5.4	0	0	0	3.6	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
	Constipation (0204)	0	0	0	3.6	1	1	0	5.4	1	1	0	5.3	2	0.7	0.1	2.4	0	0	0	3.6
Psychiatric (500)	Nervousness (0188)	1	1	0	5.4	1	1	0	5.4	1	1	0	5.3	3	1	0.2	2.9	0	0	0	3.6
Resistance mechanism (1830)	Moniliasis (0741)	0	0	0	3.6	1	1	0	5.4	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
Respiratory system (1100)	Bronchitis (0805)	0	0	0	3.6	1	1	0	5.4	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
	Pharyngitis (0523)	3	3	0.6	8.4	7	6.9	2.8	13.8	2	2	0.2	6.9	12	3.9	2.1	6.8	2	2	0.2	7
	Pneumonia (0528)	1	1	0	5.4	6	5.9	2.2	12.5	2	2	0.2	6.9	9	3	1.4	5.5	3	3	0.6	8.4

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 84: Percentage of subjects with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 243				HRV_5.2 N = 243				HRV_5.8 N = 244				Pooled HRV groups N = 730				Placebo N = 242			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	2	0.8	0.1	3
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	1	0.4	0	2.3
Central and peripheral nervous system (410)	Fever convulsions (1357)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	1	0.4	0	2.3

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 85: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 381				HRV_5.2 D = 379				HRV_5.8 D = 386				Pooled HRV groups D = 1146				Placebo D = 385			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		8	2.1	0.9	4.1	10	2.6	1.3	4.8	6	1.6	0.6	3.4	24	2.1	1.3	3.1	10	2.6	1.3	4.7
Body as a whole general (1810)	Pallor (0220)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Gastrointestinal system (600)	Gastroenteritis (0293)	3	0.8	0.2	2.3	5	1.3	0.4	3.1	1	0.3	0	1.4	9	0.8	0.4	1.5	4	1	0.3	2.6
	Gastrointestinal disorder nos (1262)	0	0	0	1	0	0	0	1	1	0.3	0	1.4	1	0.1	0	0.5	1	0.3	0	1.4
Resistance mechanism (1830)	Infection (0736)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	1	0.3	0	1.4
Respiratory system (1100)	Asthma (1367)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Bronchitis (0805)	2	0.5	0.1	1.9	3	0.8	0.2	2.3	0	0	0	1	5	0.4	0.1	1	0	0	0	1
	Pneumonia (0528)	4	1	0.3	2.7	2	0.5	0.1	1.9	4	1	0.3	2.6	10	0.9	0.4	1.6	3	0.8	0.2	2.3

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 86: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 189				HRV_5.2 D = 196				HRV_5.8 D = 192				Pooled HRV groups D = 577				Placebo D = 198			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		6	3.2	1.2	6.8	17	8.7	5.1	13.5	8	4.2	1.8	8	31	5.4	3.7	7.5	6	3	1.1	6.5
Application site (1820)	Dermatitis contact (0049)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
	Death, nos (0722)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.9	1	0.2	0	1	0	0	0	1.8
	Edema generalised (0400)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Fever (0725)	0	0	0	1.9	2	1	0.1	3.6	1	0.5	0	2.9	3	0.5	0.1	1.5	0	0	0	1.8
Central and peripheral nervous system (410)	Fever convulsions (1357)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.9	1	0.2	0	1	0	0	0	1.8
Gastrointestinal system (600)	Abdominal pain (0268)	2	1.1	0.1	3.8	3	1.5	0.3	4.4	1	0.5	0	2.9	6	1	0.4	2.2	0	0	0	1.8
	Anorexia (0165)	1	0.5	0	2.9	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
	Constipation (0204)	0	0	0	1.9	1	0.5	0	2.8	1	0.5	0	2.9	2	0.3	0	1.2	0	0	0	1.8
Psychiatric (500)	Nervousness (0188)	1	0.5	0	2.9	1	0.5	0	2.8	1	0.5	0	2.9	3	0.5	0.1	1.5	0	0	0	1.8
Resistance mechanism (1830)	Moniliasis (0741)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
Respiratory system (1100)	Bronchitis (0805)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
	Pharyngitis (0523)	3	1.6	0.3	4.6	7	3.6	1.4	7.2	2	1	0.1	3.7	12	2.1	1.1	3.6	2	1	0.1	3.6
	Pneumonia (0528)	1	0.5	0	2.9	6	3.1	1.1	6.5	2	1	0.1	3.7	9	1.6	0.7	2.9	3	1.5	0.3	4.4

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 87: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 478				HRV_5.2 D = 474				HRV_5.8 D = 477				Pooled HRV groups D = 1429				Placebo D = 476			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	2	0.4	0.1	1.5
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	1	0.2	0	1.2
Central and peripheral nervous system (410)	Fever convulsions (1357)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	1	0.2	0	1.2

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 88: Number and percentage of subjects who received vaccine dose(s) (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Total number of doses received	HRV_4.7 (N = 499)		HRV_5.2 (N = 487)		HRV_5.8 (N = 493)		Placebo (N = 486)		Total (N = 1965)	
	n	%	n	%	n	%	n	%	n	%
0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
1	21	4.2	26	5.3	22	4.5	11	2.3	80	4.1
2	478	95.8	461	94.7	471	95.5	475	97.7	1885	95.9
Any	499	100.0	487	100.0	493	100.0	486	100.0	1965	100.0

Notes: N = number of subjects in each group or in total (sum of all groups)
n/% = number/percentage of subjects receiving the specified total number of doses in each group or in total
Any = number and percentage of subjects receiving at least one dose

Supplement 89: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period (ATP cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	499	455	91.2	88.3	93.5
	HRV_5.2	487	439	90.1	87.1	92.6
	HRV_5.8	493	450	91.3	88.4	93.6
	Pooled HRV groups	1479	1344	90.9	89.3	92.3
	Placebo	486	452	93.0	90.4	95.1
Dose 2	**HRV_4.7**	478	409	85.6	82.1	88.6
	HRV_5.2	461	404	87.6	84.3	90.5
	HRV_5.8	471	414	87.9	84.6	90.7
	Pooled HRV groups	1410	1227	87.0	85.2	88.7
	Placebo	475	418	88.0	84.7	90.8
Overall/dose	**HRV_4.7**	977	864	88.4	86.3	90.4
	HRV_5.2	948	843	88.9	86.8	90.9
	HRV_5.8	964	864	89.6	87.5	91.5
	Pooled HRV groups	2889	2571	89.0	87.8	90.1
	Placebo	961	870	90.5	88.5	92.3
Overall/subject	**HRV_4.7**	499	476	95.4	93.2	97.1
	HRV_5.2	487	463	95.1	92.8	96.8
	HRV_5.8	493	469	95.1	92.8	96.9
	Pooled HRV groups	1479	1408	95.2	94.0	96.2
	Placebo	486	472	97.1	95.2	98.4

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 90: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period (ATP cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	499	110	22.0	18.5	25.9
	HRV_5.2	487	110	22.6	18.9	26.6
	HRV_5.8	493	125	25.4	21.6	29.4
	Pooled HRV groups	1479	345	23.3	21.2	25.6
	Placebo	486	116	23.9	20.1	27.9
Dose 2	**HRV_4.7**	478	99	20.7	17.2	24.6
	HRV_5.2	461	99	21.5	17.8	25.5
	HRV_5.8	471	99	21.0	17.4	25.0
	Pooled HRV groups	1410	297	21.1	19.0	23.3
	Placebo	475	98	20.6	17.1	24.6
Overall/dose	**HRV_4.7**	977	209	21.4	18.9	24.1
	HRV_5.2	948	209	22.0	19.4	24.8
	HRV_5.8	964	224	23.2	20.6	26.0
	Pooled HRV groups	2889	642	22.2	20.7	23.8
	Placebo	961	214	22.3	19.7	25.0
Overall/subject	**HRV_4.7**	499	170	34.1	29.9	38.4
	HRV_5.2	487	179	36.8	32.5	41.2
	HRV_5.8	493	174	35.3	31.1	39.7
	Pooled HRV groups	1479	523	35.4	32.9	37.9
	Placebo	486	175	36.0	31.7	40.5

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N = number of subjects having received at least one dose
n/% = number/percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 91: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period (ATP cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	499	245	49.1	44.6	53.6
	HRV_5.2	487	237	48.7	44.1	53.2
	HRV_5.8	493	240	48.7	44.2	53.2
	Pooled HRV groups	1479	722	48.8	46.2	51.4
	Placebo	486	237	48.8	44.2	53.3
Dose 2	**HRV_4.7**	478	194	40.6	36.1	45.1
	HRV_5.2	461	202	43.8	39.2	48.5
	HRV_5.8	471	213	45.2	40.7	49.8
	Pooled HRV groups	1410	609	43.2	40.6	45.8
	Placebo	475	197	41.5	37.0	46.1
Overall/dose	**HRV_4.7**	977	439	44.9	41.8	48.1
	HRV_5.2	948	439	46.3	43.1	49.5
	HRV_5.8	964	453	47.0	43.8	50.2
	Pooled HRV groups	2889	1331	46.1	44.2	47.9
	Placebo	961	434	45.2	42.0	48.4
Overall/subject	**HRV_4.7**	499	251	50.3	45.8	54.8
	HRV_5.2	487	247	50.7	46.2	55.2
	HRV_5.8	493	254	51.5	47.0	56.0
	Pooled HRV groups	1479	752	50.8	48.3	53.4
	Placebo	486	242	49.8	45.3	54.3

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N = number of subjects having received at least one dose
n/% = number/percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92: Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		1											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		499				487				493			
COUGH	Total	299	59.9	55.5	64.2	278	57.1	52.6	61.5	286	58.0	53.5	62.4
	Grade 2*3	160	32.1	28.0	36.4	131	26.9	23.0	31.1	146	29.6	25.6	33.9
	Grade 3	42	8.4	6.1	11.2	44	9.0	6.6	11.9	46	9.3	6.9	12.2
	Related	94	18.8	15.5	22.5	83	17.0	13.8	20.7	78	15.8	12.7	19.3
DIARRHEA	Total	31	6.2	4.3	8.7	27	5.5	3.7	8.0	38	7.7	5.5	10.4
	Grade 2*3	18	3.6	2.2	5.6	20	4.1	2.5	6.3	26	5.3	3.5	7.6
	Grade 3	8	1.6	0.7	3.1	9	1.8	0.8	3.5	10	2.0	1.0	3.7
	Related	14	2.8	1.5	4.7	15	3.1	1.7	5.0	27	5.5	3.6	7.9
IRRITABILITY	Total	353	70.7	66.5	74.7	335	68.8	64.5	72.9	354	71.8	67.6	75.7
	Grade 2*3	233	46.7	42.2	51.2	208	42.7	38.3	47.2	232	47.1	42.6	51.6
	Grade 3	63	12.6	9.8	15.9	62	12.7	9.9	16.0	68	13.8	10.9	17.2
	Related	212	42.5	38.1	47.0	189	38.8	34.5	43.3	212	43.0	38.6	47.5
LOSS OF APPETITE	Total	158	31.7	27.6	35.9	161	33.1	28.9	37.4	156	31.6	27.6	36.0
	Grade 2*3	49	9.8	7.4	12.8	42	8.6	6.3	11.5	62	12.6	9.8	15.8
	Grade 3	6	1.2	0.4	2.6	4	0.8	0.2	2.1	11	2.2	1.1	4.0
	Related	66	13.2	10.4	16.5	67	13.8	10.8	17.1	70	14.2	11.2	17.6
FEVER	Total	306	61.3	56.9	65.6	302	62.0	57.5	66.3	306	62.1	57.6	66.4
	Grade 2*3	113	22.6	19.0	26.6	96	19.7	16.3	23.5	115	23.3	19.7	27.3
	Grade 3	6	1.2	0.4	2.6	6	1.2	0.5	2.7	8	1.6	0.7	3.2
	Related	182	36.5	32.2	40.9	160	32.9	28.7	37.2	172	34.9	30.7	39.3
VOMITING	Total	76	15.2	12.2	18.7	89	18.3	14.9	22.0	75	15.2	12.2	18.7
	Grade 2*3	33	6.6	4.6	9.2	50	10.3	7.7	13.3	33	6.7	4.7	9.3
	Grade 3	12	2.4	1.2	4.2	19	3.9	2.4	6.0	18	3.7	2.2	5.7
	Related	39	7.8	5.6	10.5	36	7.4	5.2	10.1	33	6.7	4.7	9.3

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		1							
		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		1479				486			
COUGH	Total	863	58.4	55.8	60.9	303	62.3	57.9	66.7
	Grade 2*3	437	29.5	27.2	31.9	165	34.0	29.7	38.4
	Grade 3	132	8.9	7.5	10.5	31	6.4	4.4	8.9
	Related	255	17.2	15.3	19.3	87	17.9	14.6	21.6
DIARRHEA	Total	96	6.5	5.3	7.9	38	7.8	5.6	10.6
	Grade 2*3	64	4.3	3.3	5.5	22	4.5	2.9	6.8
	Grade 3	27	1.8	1.2	2.6	7	1.4	0.6	2.9
	Related	56	3.8	2.9	4.9	20	4.1	2.5	6.3
IRRITABILITY	Total	1042	70.5	68.1	72.8	367	75.5	71.4	79.3
	Grade 2*3	673	45.5	42.9	48.1	247	50.8	46.3	55.4
	Grade 3	193	13.0	11.4	14.9	77	15.8	12.7	19.4
	Related	613	41.4	38.9	44.0	208	42.8	38.4	47.3
LOSS OF APPETITE	Total	475	32.1	29.7	34.6	169	34.8	30.5	39.2
	Grade 2*3	153	10.3	8.8	12.0	57	11.7	9.0	14.9
	Grade 3	21	1.4	0.9	2.2	8	1.6	0.7	3.2
	Related	203	13.7	12.0	15.6	72	14.8	11.8	18.3
FEVER	Total	914	61.8	59.3	64.3	309	63.6	59.1	67.9
	Grade 2*3	324	21.9	19.8	24.1	107	22.0	18.4	26.0
	Grade 3	20	1.4	0.8	2.1	10	2.1	1.0	3.8
	Related	514	34.8	32.3	37.2	163	33.5	29.3	37.9
VOMITING	Total	240	16.2	14.4	18.2	73	15.0	12.0	18.5
	Grade 2*3	116	7.8	6.5	9.3	34	7.0	4.9	9.6
	Grade 3	49	3.3	2.5	4.4	9	1.9	0.9	3.5
	Related	108	7.3	6.0	8.7	43	8.8	6.5	11.7

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Dose		2											
Group		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		478				461				471			
COUGH	Total	291	60.9	56.3	65.3	291	63.1	58.5	67.5	305	64.8	60.3	69.1
	Grade 2*3	158	33.1	28.8	37.5	150	32.5	28.3	37.0	164	34.8	30.5	39.3
	Grade 3	48	10.0	7.5	13.1	48	10.4	7.8	13.6	49	10.4	7.8	13.5
	Related	85	17.8	14.5	21.5	97	21.0	17.4	25.1	95	20.2	16.6	24.1
DIARRHEA	Total	36	7.5	5.3	10.3	32	6.9	4.8	9.7	41	8.7	6.3	11.6
	Grade 2*3	28	5.9	3.9	8.4	21	4.6	2.8	6.9	27	5.7	3.8	8.2
	Grade 3	7	1.5	0.6	3.0	10	2.2	1.0	4.0	13	2.8	1.5	4.7
	Related	17	3.6	2.1	5.6	22	4.8	3.0	7.1	19	4.0	2.4	6.2
IRRITABILITY	Total	276	57.7	53.2	62.2	274	59.4	54.8	64.0	287	60.9	56.4	65.4
	Grade 2*3	153	32.0	27.8	36.4	151	32.8	28.5	37.2	174	36.9	32.6	41.5
	Grade 3	50	10.5	7.9	13.6	39	8.5	6.1	11.4	44	9.3	6.9	12.3
	Related	155	32.4	28.2	36.8	148	32.1	27.9	36.6	158	33.5	29.3	38.0
LOSS OF APPETITE	Total	139	29.1	25.0	33.4	135	29.3	25.2	33.7	137	29.1	25.0	33.4
	Grade 2*3	63	13.2	10.3	16.5	58	12.6	9.7	16.0	57	12.1	9.3	15.4
	Grade 3	13	2.7	1.5	4.6	16	3.5	2.0	5.6	4	0.8	0.2	2.2
	Related	51	10.7	8.0	13.8	48	10.4	7.8	13.6	46	9.8	7.2	12.8
FEVER	Total	257	53.8	49.2	58.3	244	52.9	48.3	57.6	260	55.2	50.6	59.8
	Grade 2*3	98	20.5	17.0	24.4	102	22.1	18.4	26.2	103	21.9	18.2	25.9
	Grade 3	7	1.5	0.6	3.0	11	2.4	1.2	4.2	14	3.0	1.6	4.9
	Related	123	25.7	21.9	29.9	109	23.6	19.8	27.8	131	27.8	23.8	32.1
VOMITING	Total	51	10.7	8.0	13.8	54	11.7	8.9	15.0	56	11.9	9.1	15.2
	Grade 2*3	24	5.0	3.2	7.4	31	6.7	4.6	9.4	28	5.9	4.0	8.5
	Grade 3	12	2.5	1.3	4.3	17	3.7	2.2	5.8	14	3.0	1.6	4.9
	Related	28	5.9	3.9	8.4	25	5.4	3.5	7.9	21	4.5	2.8	6.7

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		2							
		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		1410				475			
COUGH	Total	887	62.9	60.3	65.4	298	62.7	58.2	67.1
	Grade 2*3	472	33.5	31.0	36.0	175	36.8	32.5	41.4
	Grade 3	145	10.3	8.7	12.0	44	9.3	6.8	12.2
	Related	277	19.6	17.6	21.8	93	19.6	16.1	23.4
DIARRHEA	Total	109	7.7	6.4	9.2	42	8.8	6.4	11.8
	Grade 2*3	76	5.4	4.3	6.7	30	6.3	4.3	8.9
	Grade 3	30	2.1	1.4	3.0	13	2.7	1.5	4.6
	Related	58	4.1	3.1	5.3	20	4.2	2.6	6.4
IRRITABILITY	Total	837	59.4	56.7	61.9	278	58.5	53.9	63.0
	Grade 2*3	478	33.9	31.4	36.4	165	34.7	30.5	39.2
	Grade 3	133	9.4	8.0	11.1	38	8.0	5.7	10.8
	Related	461	32.7	30.2	35.2	145	30.5	26.4	34.9
LOSS OF APPETITE	Total	411	29.1	26.8	31.6	134	28.2	24.2	32.5
	Grade 2*3	178	12.6	10.9	14.5	62	13.1	10.2	16.4
	Grade 3	33	2.3	1.6	3.3	11	2.3	1.2	4.1
	Related	145	10.3	8.7	12.0	50	10.5	7.9	13.6
FEVER	Total	761	54.0	51.3	56.6	268	56.4	51.8	60.9
	Grade 2*3	303	21.5	19.4	23.7	87	18.3	14.9	22.1
	Grade 3	32	2.3	1.6	3.2	11	2.3	1.2	4.1
	Related	363	25.7	23.5	28.1	113	23.8	20.0	27.9
VOMITING	Total	161	11.4	9.8	13.2	53	11.2	8.5	14.3
	Grade 2*3	83	5.9	4.7	7.2	26	5.5	3.6	7.9
	Grade 3	43	3.0	2.2	4.1	14	2.9	1.6	4.9
	Related	74	5.2	4.1	6.5	20	4.2	2.6	6.4

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/Dose											
Group		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		977				948				964			
COUGH	Total	590	60.4	57.2	63.5	569	60.0	56.8	63.2	591	61.3	58.1	64.4
	Grade 2*3	318	32.5	29.6	35.6	281	29.6	26.7	32.7	310	32.2	29.2	35.2
	Grade 3	90	9.2	7.5	11.2	92	9.7	7.9	11.8	95	9.9	8.0	11.9
	Related	179	18.3	15.9	20.9	180	19.0	16.5	21.6	173	17.9	15.6	20.5
DIARRHEA	Total	67	6.9	5.4	8.6	59	6.2	4.8	8.0	79	8.2	6.5	10.1
	Grade 2*3	46	4.7	3.5	6.2	41	4.3	3.1	5.8	53	5.5	4.1	7.1
	Grade 3	15	1.5	0.9	2.5	19	2.0	1.2	3.1	23	2.4	1.5	3.6
	Related	31	3.2	2.2	4.5	37	3.9	2.8	5.3	46	4.8	3.5	6.3
IRRITABILITY	Total	629	64.4	61.3	67.4	609	64.2	61.1	67.3	641	66.5	63.4	69.5
	Grade 2*3	386	39.5	36.4	42.7	359	37.9	34.8	41.0	406	42.1	39.0	45.3
	Grade 3	113	11.6	9.6	13.7	101	10.7	8.8	12.8	112	11.6	9.7	13.8
	Related	367	37.6	34.5	40.7	337	35.5	32.5	38.7	370	38.4	35.3	41.5
LOSS OF APPETITE	Total	297	30.4	27.5	33.4	296	31.2	28.3	34.3	293	30.4	27.5	33.4
	Grade 2*3	112	11.5	9.5	13.6	100	10.5	8.7	12.7	119	12.3	10.3	14.6
	Grade 3	19	1.9	1.2	3.0	20	2.1	1.3	3.2	15	1.6	0.9	2.6
	Related	117	12.0	10.0	14.2	115	12.1	10.1	14.4	116	12.0	10.0	14.3
FEVER	Total	563	57.6	54.5	60.7	546	57.6	54.4	60.8	566	58.7	55.5	61.8
	Grade 2*3	211	21.6	19.1	24.3	198	20.9	18.3	23.6	218	22.6	20.0	25.4
	Grade 3	13	1.3	0.7	2.3	17	1.8	1.0	2.9	22	2.3	1.4	3.4
	Related	305	31.2	28.3	34.2	269	28.4	25.5	31.4	303	31.4	28.5	34.5
VOMITING	Total	127	13.0	11.0	15.3	143	15.1	12.9	17.5	131	13.6	11.5	15.9
	Grade 2*3	57	5.8	4.4	7.5	81	8.5	6.8	10.5	61	6.3	4.9	8.1
	Grade 3	24	2.5	1.6	3.6	36	3.8	2.7	5.2	32	3.3	2.3	4.7
	Related	67	6.9	5.4	8.6	61	6.4	5.0	8.2	54	5.6	4.2	7.2

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

		Overall/Dose							
Group		**Pooled HRV groups**				**Placebo**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
N		2889				961			
COUGH	**Total**	1750	60.6	58.8	62.4	601	62.5	59.4	65.6
	Grade 2*3	909	31.5	29.8	33.2	340	35.4	32.4	38.5
	Grade 3	277	9.6	8.5	10.7	75	7.8	6.2	9.7
	Related	532	18.4	17.0	19.9	180	18.7	16.3	21.3
DIARRHEA	**Total**	205	7.1	6.2	8.1	80	8.3	6.7	10.3
	Grade 2*3	140	4.8	4.1	5.7	52	5.4	4.1	7.0
	Grade 3	57	2.0	1.5	2.5	20	2.1	1.3	3.2
	Related	114	3.9	3.3	4.7	40	4.2	3.0	5.6
IRRITABILITY	**Total**	1879	65.0	63.3	66.8	645	67.1	64.0	70.1
	Grade 2*3	1151	39.8	38.0	41.7	412	42.9	39.7	46.1
	Grade 3	326	11.3	10.2	12.5	115	12.0	10.0	14.2
	Related	1074	37.2	35.4	39.0	353	36.7	33.7	39.9
LOSS OF APPETITE	**Total**	886	30.7	29.0	32.4	303	31.5	28.6	34.6
	Grade 2*3	331	11.5	10.3	12.7	119	12.4	10.4	14.6
	Grade 3	54	1.9	1.4	2.4	19	2.0	1.2	3.1
	Related	348	12.0	10.9	13.3	122	12.7	10.7	15.0
FEVER	**Total**	1675	58.0	56.2	59.8	577	60.0	56.9	63.2
	Grade 2*3	627	21.7	20.2	23.3	194	20.2	17.7	22.9
	Grade 3	52	1.8	1.3	2.4	21	2.2	1.4	3.3
	Related	877	30.4	28.7	32.1	276	28.7	25.9	31.7
VOMITING	**Total**	401	13.9	12.6	15.2	126	13.1	11.0	15.4
	Grade 2*3	199	6.9	6.0	7.9	60	6.2	4.8	8.0
	Grade 3	92	3.2	2.6	3.9	23	2.4	1.5	3.6
	Related	182	6.3	5.4	7.2	63	6.6	5.1	8.3

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/Subject											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		499				487				493			
COUGH	Total	388	77.8	73.8	81.3	377	77.4	73.4	81.1	383	77.7	73.8	81.3
	Grade 2*3	235	47.1	42.6	51.6	224	46.0	41.5	50.5	234	47.5	43.0	52.0
	Grade 3	82	16.4	13.3	20.0	82	16.8	13.6	20.5	80	16.2	13.1	19.8
	Related	135	27.1	23.2	31.2	144	29.6	25.5	33.8	142	28.8	24.8	33.0
DIARRHEA	Total	64	12.8	10.0	16.1	53	10.9	8.3	14.0	68	13.8	10.9	17.2
	Grade 2*3	44	8.8	6.5	11.7	39	8.0	5.8	10.8	48	9.7	7.3	12.7
	Grade 3	15	3.0	1.7	4.9	19	3.9	2.4	6.0	22	4.5	2.8	6.7
	Related	31	6.2	4.3	8.7	35	7.2	5.1	9.9	41	8.3	6.0	11.1
IRRITABILITY	Total	390	78.2	74.3	81.7	389	79.9	76.0	83.3	401	81.3	77.6	84.7
	Grade 2*3	283	56.7	52.2	61.1	270	55.4	50.9	59.9	286	58.0	53.5	62.4
	Grade 3	92	18.4	15.1	22.1	88	18.1	14.8	21.8	87	17.6	14.4	21.3
	Related	228	45.7	41.3	50.2	212	43.5	39.1	48.1	236	47.9	43.4	52.4
LOSS OF APPETITE	Total	224	44.9	40.5	49.4	223	45.8	41.3	50.3	215	43.6	39.2	48.1
	Grade 2*3	98	19.6	16.2	23.4	86	17.7	14.4	21.3	100	20.3	16.8	24.1
	Grade 3	17	3.4	2.0	5.4	18	3.7	2.2	5.8	15	3.0	1.7	5.0
	Related	97	19.4	16.1	23.2	92	18.9	15.5	22.7	92	18.7	15.3	22.4
FEVER	Total	380	76.2	72.2	79.8	376	77.2	73.2	80.9	372	75.5	71.4	79.2
	Grade 2*3	175	35.1	30.9	39.4	169	34.7	30.5	39.1	179	36.3	32.1	40.7
	Grade 3	13	2.6	1.4	4.4	17	3.5	2.0	5.5	21	4.3	2.7	6.4
	Related	209	41.9	37.5	46.4	188	38.6	34.3	43.1	203	41.2	36.8	45.7
VOMITING	Total	107	21.4	17.9	25.3	125	25.7	21.8	29.8	113	22.9	19.3	26.9
	Grade 2*3	49	9.8	7.4	12.8	73	15.0	11.9	18.5	57	11.6	8.9	14.7
	Grade 3	23	4.6	2.9	6.8	35	7.2	5.1	9.9	30	6.1	4.1	8.6
	Related	55	11.0	8.4	14.1	56	11.5	8.8	14.7	48	9.7	7.3	12.7

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

		Overall/Subject							
Group		**Pooled HRV groups**				**Placebo**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
N		1479				486			
COUGH	**Total**	1148	77.6	75.4	79.7	389	80.0	76.2	83.5
	Grade 2*3	693	46.9	44.3	49.4	260	53.5	49.0	58.0
	Grade 3	244	16.5	14.6	18.5	68	14.0	11.0	17.4
	Related	421	28.5	26.2	30.8	139	28.6	24.6	32.8
DIARRHEA	**Total**	185	12.5	10.9	14.3	74	15.2	12.1	18.7
	Grade 2*3	131	8.9	7.5	10.4	50	10.3	7.7	13.3
	Grade 3	56	3.8	2.9	4.9	18	3.7	2.2	5.8
	Related	107	7.2	6.0	8.7	38	7.8	5.6	10.6
IRRITABILITY	**Total**	1180	79.8	77.6	81.8	401	82.5	78.8	85.8
	Grade 2*3	839	56.7	54.2	59.3	300	61.7	57.2	66.1
	Grade 3	267	18.1	16.1	20.1	103	21.2	17.6	25.1
	Related	676	45.7	43.1	48.3	222	45.7	41.2	50.2
LOSS OF APPETITE	**Total**	662	44.8	42.2	47.3	226	46.5	42.0	51.0
	Grade 2*3	284	19.2	17.2	21.3	100	20.6	17.1	24.4
	Grade 3	50	3.4	2.5	4.4	19	3.9	2.4	6.0
	Related	281	19.0	17.0	21.1	97	20.0	16.5	23.8
FEVER	**Total**	1128	76.3	74.0	78.4	384	79.0	75.1	82.5
	Grade 2*3	523	35.4	32.9	37.9	160	32.9	28.8	37.3
	Grade 3	51	3.4	2.6	4.5	20	4.1	2.5	6.3
	Related	600	40.6	38.1	43.1	193	39.7	35.3	44.2
VOMITING	**Total**	345	23.3	21.2	25.6	110	22.6	19.0	26.6
	Grade 2*3	179	12.1	10.5	13.9	54	11.1	8.5	14.2
	Grade 3	88	5.9	4.8	7.3	22	4.5	2.9	6.8
	Related	159	10.8	9.2	12.4	56	11.5	8.8	14.7

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 93: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		322	64.5	60.2	68.7	309	63.4	59	67.7	296	60	55.6	64.4	927	62.7	60.2	65.1	304	62.6	58.1	66.9
Application site (1820)	Dermatitis contact (0049)	4	0.8	0.2	2	8	1.6	0.7	3.2	3	0.6	0.1	1.8	15	1	0.6	1.7	6	1.2	0.5	2.7
	Injection site reaction (0058)	7	1.4	0.6	2.9	4	0.8	0.2	2.1	5	1	0.3	2.4	16	1.1	0.6	1.8	5	1	0.3	2.4
	Otitis externa (0059)	0	0	0	0.7	0	0	0	0.8	1	0.2	0	1.1	1	0.1	0	0.4	0	0	0	0.8
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.7	2	0.4	0	1.5	1	0.2	0	1.1	3	0.2	0	0.6	1	0.2	0	1.1
	Allergic reaction (0712)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	3	0.6	0.1	1.8
	Allergy (1058)	3	0.6	0.1	1.7	6	1.2	0.5	2.7	5	1	0.3	2.4	14	0.9	0.5	1.6	8	1.6	0.7	3.2
	Death, nos (0722)	0	0	0	0.7	0	0	0	0.8	1	0.2	0	1.1	1	0.1	0	0.4	0	0	0	0.8
	Fever (0725)	40	8	5.8	10.8	36	7.4	5.2	10.1	40	8.1	5.9	10.9	116	7.8	6.5	9.3	32	6.6	4.5	9.2
	Injury (9001)	4	0.8	0.2	2	0	0	0	0.8	0	0	0	0.7	4	0.3	0.1	0.7	0	0	0	0.8
Cardiovascular general (1010)	Cyanosis (0501)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	0.7	2	0.4	0	1.5	0	0	0	0.7	2	0.1	0	0.5	1	0.2	0	1.1
	Fever convulsions (1357)	1	0.2	0	1.1	0	0	0	0.8	1	0.2	0	1.1	2	0.1	0	0.5	0	0	0	0.8
	Spasm generalized (0149)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 93 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
	Vascular malformation peripheral (0764)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
Gastrointestinal system (600)	Abdominal pain (0268)	30	6	4.1	8.5	25	5.1	3.3	7.5	23	4.7	3	6.9	78	5.3	4.2	6.5	22	4.5	2.9	6.8
	Anorexia (0165)	18	3.6	2.2	5.6	17	3.5	2	5.5	12	2.4	1.3	4.2	47	3.2	2.3	4.2	21	4.3	2.7	6.5
	Anus disorder (0269)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Constipation (0204)	10	2	1	3.7	10	2.1	1	3.7	9	1.8	0.8	3.4	29	2	1.3	2.8	5	1	0.3	2.4
	Gastroenteritis (0293)	2	0.4	0	1.4	5	1	0.3	2.4	1	0.2	0	1.1	8	0.5	0.2	1.1	2	0.4	0	1.5
	Gastroesophageal reflux (1149)	4	0.8	0.2	2	6	1.2	0.5	2.7	7	1.4	0.6	2.9	17	1.1	0.7	1.8	3	0.6	0.1	1.8
	Gastrointestinal disorder nos (1262)	0	0	0	0.7	0	0	0	0.8	1	0.2	0	1.1	1	0.1	0	0.4	0	0	0	0.8
	Stomatitis (0327)	0	0	0	0.7	1	0.2	0	1.1	1	0.2	0	1.1	2	0.1	0	0.5	1	0.2	0	1.1
	Stomatitis aphthous (0751)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
	Vomiting (0228)	13	2.6	1.4	4.4	16	3.3	1.9	5.3	12	2.4	1.3	4.2	41	2.8	2	3.7	18	3.7	2.2	5.8
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Earache (0260)	2	0.4	0	1.4	1	0.2	0	1.1	1	0.2	0	1.1	4	0.3	0.1	0.7	1	0.2	0	1.1
Neoplasm (1700)	Neoplasm nos (1259)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
Psychiatric (500)	Nervousness (0188)	26	5.2	3.4	7.5	22	4.5	2.9	6.8	26	5.3	3.5	7.6	74	5	3.9	6.2	32	6.6	4.5	9.2

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 93 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Red blood cell (1210)	Anemia (0544)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
Resistance mechanism (1830)	Abscess (0887)	1	0.2	0	1.1	1	0.2	0	1.1	3	0.6	0.1	1.8	5	0.3	0.1	0.8	0	0	0	0.8
	Infection (0736)	26	5.2	3.4	7.5	19	3.9	2.4	6	17	3.4	2	5.5	62	4.2	3.2	5.3	20	4.1	2.5	6.3
	Infection bacterial (0738)	1	0.2	0	1.1	2	0.4	0	1.5	0	0	0	0.7	3	0.2	0	0.6	1	0.2	0	1.1
	Infection viral (0740)	159	31.9	27.8	36.2	142	29.2	25.2	33.4	144	29.2	25.2	33.4	445	30.1	27.8	32.5	151	31.1	27	35.4
	Moniliasis (0741)	7	1.4	0.6	2.9	10	2.1	1	3.7	3	0.6	0.1	1.8	20	1.4	0.8	2.1	4	0.8	0.2	2.1
	Otitis media (0750)	5	1	0.3	2.3	11	2.3	1.1	4	3	0.6	0.1	1.8	19	1.3	0.8	2	9	1.9	0.9	3.5
	Upper resp tract infection (0543)	39	7.8	5.6	10.5	32	6.6	4.5	9.1	40	8.1	5.9	10.9	111	7.5	6.2	9	37	7.6	5.4	10.3
Respiratory system (1100)	Asthma (1367)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Atelectasis (1197)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
	Bronchitis (0805)	19	3.8	2.3	5.9	21	4.3	2.7	6.5	20	4.1	2.5	6.2	60	4.1	3.1	5.2	12	2.5	1.3	4.3
	Bronchospasm (0511)	14	2.8	1.5	4.7	8	1.6	0.7	3.2	11	2.2	1.1	4	33	2.2	1.5	3.1	7	1.4	0.6	2.9
	Coughing (0513)	23	4.6	2.9	6.8	21	4.3	2.7	6.5	25	5.1	3.3	7.4	69	4.7	3.6	5.9	17	3.5	2.1	5.5
	Dyspnea (0514)	0	0	0	0.7	1	0.2	0	1.1	1	0.2	0	1.1	2	0.1	0	0.5	1	0.2	0	1.1
	Laryngitis (0521)	1	0.2	0	1.1	3	0.6	0.1	1.8	1	0.2	0	1.1	5	0.3	0.1	0.8	2	0.4	0	1.5
	Pharyngitis (0523)	52	10.4	7.9	13.4	64	13.1	10.3	16.5	54	11	8.3	14	170	11.5	9.9	13.2	65	13.4	10.5	16.7
	Pneumonia (0528)	13	2.6	1.4	4.4	23	4.7	3	7	19	3.9	2.3	6	55	3.7	2.8	4.8	20	4.1	2.5	6.3
	Respiratory disorder (0536)	0	0	0	0.7	5	1	0.3	2.4	1	0.2	0	1.1	6	0.4	0.1	0.9	2	0.4	0	1.5
	Rhinitis (0539)	7	1.4	0.6	2.9	13	2.7	1.4	4.5	12	2.4	1.3	4.2	32	2.2	1.5	3	11	2.3	1.1	4
	Sputum increased (0541)	3	0.6	0.1	1.7	7	1.4	0.6	2.9	1	0.2	0	1.1	11	0.7	0.4	1.3	3	0.6	0.1	1.8

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 93 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Secondary term (2000)	Varicella (1516)	2	0.4	0	1.4	1	0.2	0	1.1	1	0.2	0	1.1	4	0.3	0.1	0.7	4	0.8	0.2	2.1
Skin and appendages (100)	Dermatitis (0007)	2	0.4	0	1.4	4	0.8	0.2	2.1	5	1	0.3	2.4	11	0.7	0.4	1.3	0	0	0	0.8
	Dermatitis fungal (0009)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Furunculosis (0016)	2	0.4	0	1.4	0	0	0	0.8	1	0.2	0	1.1	3	0.2	0	0.6	0	0	0	0.8
	Photosensitivity reaction (0022)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
	Pruritus (0024)	0	0	0	0.7	3	0.6	0.1	1.8	2	0.4	0	1.5	5	0.3	0.1	0.8	0	0	0	0.8
	Rash (0027)	1	0.2	0	1.1	1	0.2	0	1.1	0	0	0	0.7	2	0.1	0	0.5	0	0	0	0.8
	Rash erythematous (0028)	2	0.4	0	1.4	1	0.2	0	1.1	0	0	0	0.7	3	0.2	0	0.6	1	0.2	0	1.1
	Rash maculo-papular (0030)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	1	0.2	0	1.1
	Rash pustular (0032)	0	0	0	0.7	2	0.4	0	1.5	3	0.6	0.1	1.8	5	0.3	0.1	0.8	2	0.4	0	1.5
	Seborrhea (0033)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Skin disorder (0037)	4	0.8	0.2	2	7	1.4	0.6	2.9	8	1.6	0.7	3.2	19	1.3	0.8	2	7	1.4	0.6	2.9
	Sweat gland disorder (1166)	1	0.2	0	1.1	1	0.2	0	1.1	2	0.4	0	1.5	4	0.3	0.1	0.7	0	0	0	0.8
Urinary system (1300)	Dysuria (0601)	0	0	0	0.7	1	0.2	0	1.1	2	0.4	0	1.5	3	0.2	0	0.6	0	0	0	0.8
	Urinary tract infection (0628)	0	0	0	0.7	0	0	0	0.8	2	0.4	0	1.5	2	0.1	0	0.5	2	0.4	0	1.5
Vision (431)	Blepharitis (1007)	1	0.2	0	1.1	0	0	0	0.8	1	0.2	0	1.1	2	0.1	0	0.5	0	0	0	0.8
	Conjunctivitis (0238)	12	2.4	1.2	4.2	13	2.7	1.4	4.5	9	1.8	0.8	3.4	34	2.3	1.6	3.2	9	1.9	0.9	3.5
White cell and reticuloendothelial system (1220)	Lymphadenopathy cervical (0578)	0	0	0	0.7	0	0	0	0.8	1	0.2	0	1.1	1	0.1	0	0.4	0	0	0	0.8

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 94: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		443	45.3	42.2	48.5	426	44.9	41.7	48.2	416	43.2	40	46.3	1285	44.5	42.7	46.3	419	43.6	40.4	46.8
Application site (1820)	Dermatitis contact (0049)	4	0.4	0.1	1	8	0.8	0.4	1.7	3	0.3	0.1	0.9	15	0.5	0.3	0.9	7	0.7	0.3	1.5
	Injection site reaction (0058)	7	0.7	0.3	1.5	4	0.4	0.1	1.1	5	0.5	0.2	1.2	16	0.6	0.3	0.9	6	0.6	0.2	1.4
	Otitis externa (0059)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.6	1	0	0	0.2	0	0	0	0.4
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.4	2	0.2	0	0.8	1	0.1	0	0.6	3	0.1	0	0.3	1	0.1	0	0.6
	Allergic reaction (0712)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	3	0.3	0.1	0.9
	Allergy (1058)	3	0.3	0.1	0.9	7	0.7	0.3	1.5	5	0.5	0.2	1.2	15	0.5	0.3	0.9	8	0.8	0.4	1.6
	Death, nos (0722)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.6	1	0	0	0.2	0	0	0	0.4
	Fever (0725)	41	4.2	3	5.7	38	4	2.9	5.5	42	4.4	3.2	5.8	121	4.2	3.5	5	34	3.5	2.5	4.9
	Injury (9001)	4	0.4	0.1	1	0	0	0	0.4	0	0	0	0.4	4	0.1	0	0.4	0	0	0	0.4
Cardiovascular general (1010)	Cyanosis (0501)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	0.4	2	0.2	0	0.8	0	0	0	0.4	2	0.1	0	0.2	1	0.1	0	0.6
	Fever convulsions (1357)	1	0.1	0	0.6	0	0	0	0.4	1	0.1	0	0.6	2	0.1	0	0.2	0	0	0	0.4
	Spasm generalized (0149)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
	Vascular malformation peripheral (0764)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 94 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Gastrointestinal system (600)	Abdominal pain (0268)	32	3.3	2.3	4.6	26	2.7	1.8	4	28	2.9	1.9	4.2	86	3	2.4	3.7	22	2.3	1.4	3.4
	Anorexia (0165)	21	2.1	1.3	3.3	19	2	1.2	3.1	12	1.2	0.6	2.2	52	1.8	1.3	2.4	22	2.3	1.4	3.4
	Anus disorder (0269)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Constipation (0204)	10	1	0.5	1.9	11	1.2	0.6	2.1	10	1	0.5	1.9	31	1.1	0.7	1.5	5	0.5	0.2	1.2
	Gastroenteritis (0293)	2	0.2	0	0.7	5	0.5	0.2	1.2	1	0.1	0	0.6	8	0.3	0.1	0.5	2	0.2	0	0.7
	Gastroesophageal reflux (1149)	4	0.4	0.1	1	6	0.6	0.2	1.4	7	0.7	0.3	1.5	17	0.6	0.3	0.9	3	0.3	0.1	0.9
	Gastrointestinal disorder nos (1262)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.6	1	0	0	0.2	0	0	0	0.4
	Stomatitis (0327)	0	0	0	0.4	1	0.1	0	0.6	1	0.1	0	0.6	2	0.1	0	0.2	1	0.1	0	0.6
	Stomatitis aphthous (0751)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
	Vomiting (0228)	13	1.3	0.7	2.3	17	1.8	1	2.9	12	1.2	0.6	2.2	42	1.5	1	2	18	1.9	1.1	2.9
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Earache (0260)	2	0.2	0	0.7	1	0.1	0	0.6	1	0.1	0	0.6	4	0.1	0	0.4	1	0.1	0	0.6
Neoplasm (1700)	Neoplasm nos (1259)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
Psychiatric (500)	Nervousness (0188)	35	3.6	2.5	4.9	26	2.7	1.8	4	29	3	2	4.3	90	3.1	2.5	3.8	35	3.6	2.5	5
Red blood cell (1210)	Anemia (0544)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 94 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Resistance mechanism (1830)	Abscess (0887)	1	0.1	0	0.6	1	0.1	0	0.6	3	0.3	0.1	0.9	5	0.2	0.1	0.4	0	0	0	0.4
	Infection (0736)	27	2.8	1.8	4	20	2.1	1.3	3.2	17	1.8	1	2.8	64	2.2	1.7	2.8	20	2.1	1.3	3.2
	Infection bacterial (0738)	1	0.1	0	0.6	2	0.2	0	0.8	0	0	0	0.4	3	0.1	0	0.3	1	0.1	0	0.6
	Infection viral (0740)	181	18.5	16.1	21.1	161	17	14.6	19.5	172	17.8	15.5	20.4	514	17.8	16.4	19.2	180	18.7	16.3	21.3
	Moniliasis (0741)	7	0.7	0.3	1.5	10	1.1	0.5	1.9	3	0.3	0.1	0.9	20	0.7	0.4	1.1	4	0.4	0.1	1.1
	Otitis media (0750)	5	0.5	0.2	1.2	11	1.2	0.6	2.1	3	0.3	0.1	0.9	19	0.7	0.4	1	9	0.9	0.4	1.8
	Upper resp tract infection (0543)	45	4.6	3.4	6.1	33	3.5	2.4	4.9	45	4.7	3.4	6.2	123	4.3	3.6	5.1	39	4.1	2.9	5.5
Respiratory system (1100)	Asthma (1367)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Atelectasis (1197)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
	Bronchitis (0805)	19	1.9	1.2	3	21	2.2	1.4	3.4	20	2.1	1.3	3.2	60	2.1	1.6	2.7	12	1.2	0.6	2.2
Respiratory system (1100)	Bronchospasm (0511)	14	1.4	0.8	2.4	8	0.8	0.4	1.7	11	1.1	0.6	2	33	1.1	0.8	1.6	8	0.8	0.4	1.6
	Coughing (0513)	27	2.8	1.8	4	21	2.2	1.4	3.4	27	2.8	1.9	4	75	2.6	2	3.2	18	1.9	1.1	2.9
	Dyspnea (0514)	0	0	0	0.4	1	0.1	0	0.6	1	0.1	0	0.6	2	0.1	0	0.2	1	0.1	0	0.6
	Laryngitis (0521)	1	0.1	0	0.6	3	0.3	0.1	0.9	1	0.1	0	0.6	5	0.2	0.1	0.4	2	0.2	0	0.7
	Pharyngitis (0523)	68	7	5.4	8.7	88	9.3	7.5	11.3	68	7.1	5.5	8.9	224	7.8	6.8	8.8	80	8.3	6.7	10.3
	Pneumonia (0528)	13	1.3	0.7	2.3	23	2.4	1.5	3.6	20	2.1	1.3	3.2	56	1.9	1.5	2.5	20	2.1	1.3	3.2
	Respiratory disorder (0536)	0	0	0	0.4	6	0.6	0.2	1.4	1	0.1	0	0.6	7	0.2	0.1	0.5	2	0.2	0	0.7
	Rhinitis (0539)	7	0.7	0.3	1.5	13	1.4	0.7	2.3	13	1.3	0.7	2.3	33	1.1	0.8	1.6	11	1.1	0.6	2
	Sputum increased (0541)	3	0.3	0.1	0.9	8	0.8	0.4	1.7	1	0.1	0	0.6	12	0.4	0.2	0.7	3	0.3	0.1	0.9
Secondary term (2000)	Varicella (1516)	2	0.2	0	0.7	1	0.1	0	0.6	1	0.1	0	0.6	4	0.1	0	0.4	4	0.4	0.1	1.1

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 94 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Skin and appendages (100)	Dermatitis (0007)	2	0.2	0	0.7	4	0.4	0.1	1.1	5	0.5	0.2	1.2	11	0.4	0.2	0.7	0	0	0	0.4
	Dermatitis fungal (0009)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Furunculosis (0016)	2	0.2	0	0.7	0	0	0	0.4	1	0.1	0	0.6	3	0.1	0	0.3	0	0	0	0.4
	Photosensitivity reaction (0022)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
	Pruritus (0024)	0	0	0	0.4	3	0.3	0.1	0.9	2	0.2	0	0.7	5	0.2	0.1	0.4	0	0	0	0.4
	Rash (0027)	1	0.1	0	0.6	1	0.1	0	0.6	0	0	0	0.4	2	0.1	0	0.2	0	0	0	0.4
	Rash erythematous (0028)	2	0.2	0	0.7	1	0.1	0	0.6	0	0	0	0.4	3	0.1	0	0.3	1	0.1	0	0.6
	Rash maculo-papular (0030)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	1	0.1	0	0.6
	Rash pustular (0032)	0	0	0	0.4	2	0.2	0	0.8	3	0.3	0.1	0.9	5	0.2	0.1	0.4	2	0.2	0	0.7
	Seborrhea (0033)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Skin disorder (0037)	4	0.4	0.1	1	7	0.7	0.3	1.5	9	0.9	0.4	1.8	20	0.7	0.4	1.1	7	0.7	0.3	1.5
	Sweat gland disorder (1166)	1	0.1	0	0.6	1	0.1	0	0.6	2	0.2	0	0.7	4	0.1	0	0.4	0	0	0	0.4
Urinary system (1300)	Dysuria (0601)	0	0	0	0.4	1	0.1	0	0.6	2	0.2	0	0.7	3	0.1	0	0.3	0	0	0	0.4
	Urinary tract infection (0628)	0	0	0	0.4	0	0	0	0.4	2	0.2	0	0.7	2	0.1	0	0.2	3	0.3	0.1	0.9
Vision (431)	Blepharitis (1007)	1	0.1	0	0.6	0	0	0	0.4	1	0.1	0	0.6	2	0.1	0	0.2	0	0	0	0.4
	Conjunctivitis (0238)	12	1.2	0.6	2.1	13	1.4	0.7	2.3	9	0.9	0.4	1.8	34	1.2	0.8	1.6	9	0.9	0.4	1.8
White cell and reticuloendothelial system (1220)	Lymphadenopathy cervical (0578)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.6	1	0	0	0.2	0	0	0	0.4

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 95: Percentage of subjects with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		2	0.4	0	1.4	0	0	0	0.8	0	0	0	0.7	2	0.1	0	0.5	2	0.4	0	1.5
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
	Fever (0725)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
Respiratory system (1100)	Bronchitis (0805)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8

Notes: N = number of subjects having received at least one dose
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 96: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		2	0.2	0	0.7	0	0	0	0.4	0	0	0	0.4	2	0.1	0	0.2	2	0.2	0	0.7
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
	Fever (0725)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
Respiratory system (1100)	Bronchitis (0805)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4

Notes:
D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 97: Percentage of subjects with grade "3" unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		13	2.6	1.4	4.4	25	5.1	3.3	7.5	13	2.6	1.4	4.5	51	3.4	2.6	4.5	12	2.5	1.3	4.3
Application site (1820)	Dermatitis contact (0049)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Allergic reaction (0712)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
	Death, nos (0722)	0	0	0	0.7	0	0	0	0.8	1	0.2	0	1.1	1	0.1	0	0.4	0	0	0	0.8
	Fever (0725)	0	0	0	0.7	2	0.4	0	1.5	1	0.2	0	1.1	3	0.2	0	0.6	0	0	0	0.8
Central and peripheral nervous system (410)	Fever convulsions (1357)	1	0.2	0	1.1	0	0	0	0.8	1	0.2	0	1.1	2	0.1	0	0.5	0	0	0	0.8
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
Gastrointestinal system (600)	Abdominal pain (0268)	2	0.4	0	1.4	3	0.6	0.1	1.8	1	0.2	0	1.1	6	0.4	0.1	0.9	0	0	0	0.8
	Anorexia (0165)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Constipation (0204)	0	0	0	0.7	1	0.2	0	1.1	1	0.2	0	1.1	2	0.1	0	0.5	0	0	0	0.8
Gastrointestinal system (600)	Gastroenteritis (0293)	2	0.4	0	1.4	5	1	0.3	2.4	1	0.2	0	1.1	8	0.5	0.2	1.1	2	0.4	0	1.5
	Gastrointestinal disorder nos (1262)	0	0	0	0.7	0	0	0	0.8	1	0.2	0	1.1	1	0.1	0	0.4	0	0	0	0.8

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 97 (continued): Percentage of subjects with grade "3" unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Psychiatric (500)	Nervousness (0188)	1	0.2	0	1.1	0	0	0	0.8	1	0.2	0	1.1	2	0.1	0	0.5	0	0	0	0.8
Resistance	Infection (0736)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	1	0.2	0	1.1
mechanism (1830)	Moniliasis (0741)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
Respiratory system	Asthma (1367)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
(1100)	Bronchitis (0805)	2	0.4	0	1.4	3	0.6	0.1	1.8	0	0	0	0.7	5	0.3	0.1	0.8	0	0	0	0.8
	Pharyngitis (0523)	3	0.6	0.1	1.7	6	1.2	0.5	2.7	2	0.4	0	1.5	11	0.7	0.4	1.3	2	0.4	0	1.5
	Pneumonia (0528)	4	0.8	0.2	2	7	1.4	0.6	2.9	5	1	0.3	2.4	16	1.1	0.6	1.8	6	1.2	0.5	2.7

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 98: Percentage of doses with grade "3" unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		13	1.3	0.7	2.3	25	2.6	1.7	3.9	13	1.3	0.7	2.3	51	1.8	1.3	2.3	13	1.4	0.7	2.3
Application site (1820)	Dermatitis contact (0049)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Allergic reaction (0712)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
	Death, nos (0722)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.6	1	0	0	0.2	0	0	0	0.4
	Fever (0725)	0	0	0	0.4	2	0.2	0	0.8	1	0.1	0	0.6	3	0.1	0	0.3	0	0	0	0.4
Central and peripheral nervous system (410)	Fever convulsions (1357)	1	0.1	0	0.6	0	0	0	0.4	1	0.1	0	0.6	2	0.1	0	0.2	0	0	0	0.4
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
Gastrointestinal system (600)	Abdominal pain (0268)	2	0.2	0	0.7	3	0.3	0.1	0.9	1	0.1	0	0.6	6	0.2	0.1	0.5	0	0	0	0.4
	Anorexia (0165)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Constipation (0204)	0	0	0	0.4	1	0.1	0	0.6	1	0.1	0	0.6	2	0.1	0	0.2	0	0	0	0.4
	Gastroenteritis (0293)	2	0.2	0	0.7	5	0.5	0.2	1.2	1	0.1	0	0.6	8	0.3	0.1	0.5	2	0.2	0	0.7
	Gastrointestinal disorder nos (1262)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.6	1	0	0	0.2	0	0	0	0.4

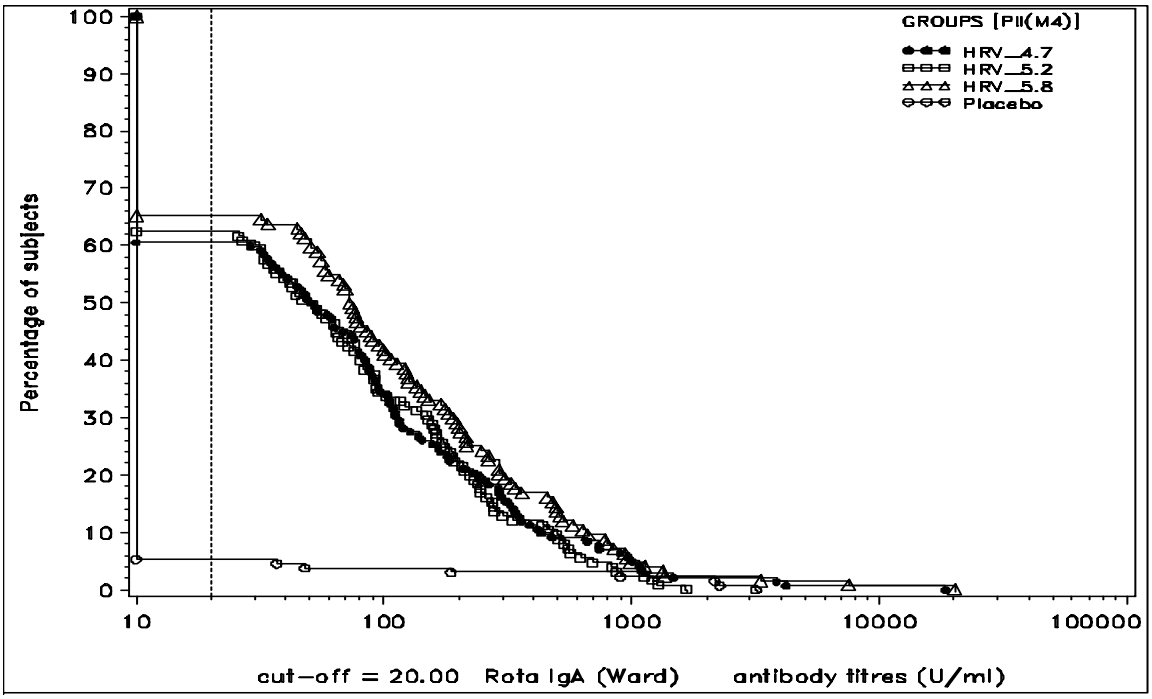
Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 98 (continued): Percentage of doses with grade "3" unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

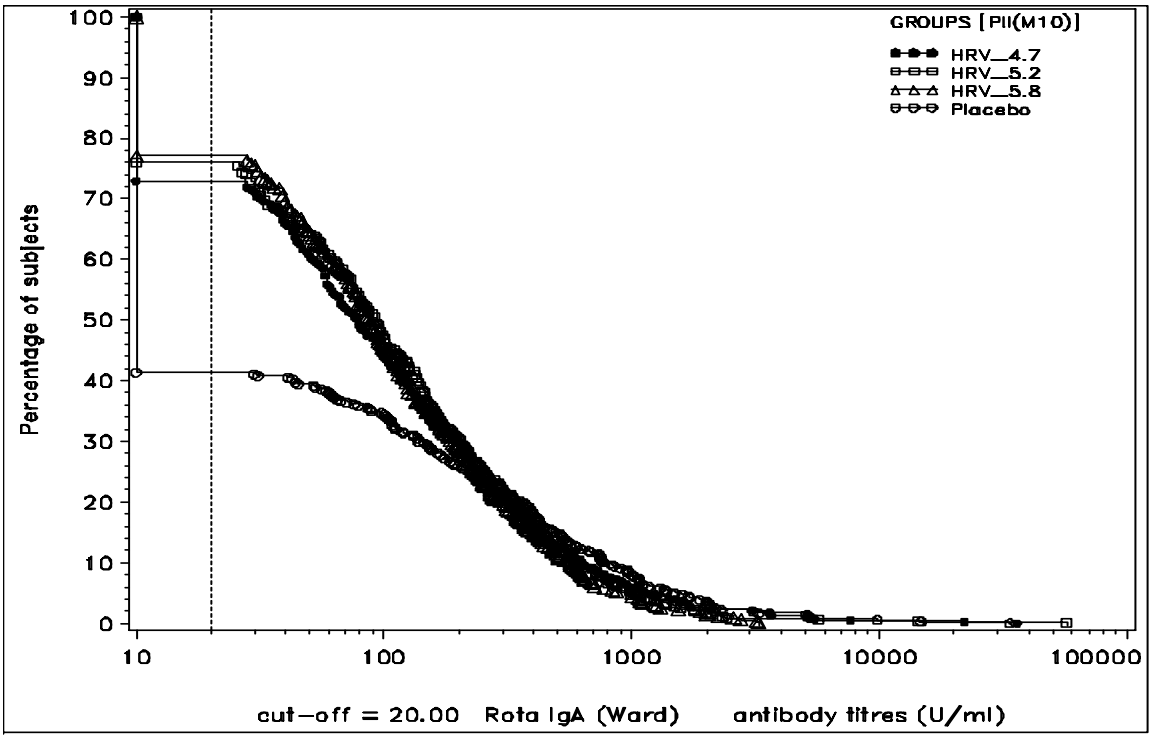
WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Psychiatric (500)	Nervousness (0188)	1	0.1	0	0.6	0	0	0	0.4	1	0.1	0	0.6	2	0.1	0	0.2	0	0	0	0.4
Resistance mechanism (1830)	Infection (0736)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	1	0.1	0	0.6
	Moniliasis (0741)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
Respiratory system (1100)	Asthma (1367)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Bronchitis (0805)	2	0.2	0	0.7	3	0.3	0.1	0.9	0	0	0	0.4	5	0.2	0.1	0.4	0	0	0	0.4
	Pharyngitis (0523)	3	0.3	0.1	0.9	6	0.6	0.2	1.4	2	0.2	0	0.7	11	0.4	0.2	0.7	2	0.2	0	0.7
	Pneumonia (0528)	4	0.4	0.1	1	7	0.7	0.3	1.5	5	0.5	0.2	1.2	16	0.6	0.3	0.9	6	0.6	0.2	1.4

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 99: Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations two months after Dose 2 (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 100: Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 101: Results of the exploratory logistic regression to assess impact of feeding criteria on the vaccine take (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Factor	Significance (2 sided P-value)
Exclusive breast feeding	0.464
Breast fed + formula fed	0.848
Fed within 1 hour before vaccination	0.725
Fed within 30 minutes after vaccination	0.273
Group	0.189

Supplement 102: Anti-rotavirus IgA antibody GMC and seroconversion rates in Brazil (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	139	0	0.0	0.0	2.6	<20	-	-
	PI(M2)	57	21	36.8	24.4	50.7	26.2	17.9	38.3
	PII(M4)	53	29	54.7	40.4	68.4	44.8	28.1	71.3
	PII(M10)	131	82	62.6	53.7	70.9	62.5	46.1	84.6
HRV_5.2	PRE	114	0	0.0	0.0	3.2	<20	-	-
	PI(M2)	46	18	39.1	25.1	54.6	28.7	18.4	44.6
	PII(M4)	39	29	74.4	57.9	87.0	84.9	50.3	143.5
	PII(M10)	110	83	75.5	66.3	83.2	93.4	67.7	129.0
HRV_5.8	PRE	120	0	0.0	0.0	3.0	<20	-	-
	PI(M2)	46	18	39.1	25.1	54.6	25.6	17.5	37.6
	PII(M4)	44	28	63.6	47.8	77.6	57.2	35.7	91.6
	PII(M10)	119	80	67.2	58.0	75.6	72.0	53.4	97.1
Pooled HRV groups	PRE	373	0	0.0	0.0	1.0	<20	-	-
	PI(M2)	149	57	38.3	30.4	46.6	26.7	21.3	33.6
	PII(M4)	136	86	63.2	54.5	71.3	58.2	44.1	76.8
	PII(M10)	360	245	68.1	63.0	72.8	74.1	62.0	88.4
Placebo	PRE	116	0	0.0	0.0	3.1	<20	-	-
	PI(M2)	49	3	6.1	1.3	16.9	<20	-	-
	PII(M4)	47	5	10.6	3.5	23.1	<20	-	-
	PII(M10)	112	40	35.7	26.9	45.3	39.5	27.1	57.5

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = two months after the Dose 1
PII(M 4) = two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 103: Anti-rotavirus IgA antibody GMC and seroconversion rates in Mexico (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	76	0	0.0	0.0	4.7	<20	-	-
	PI(M2)	46	22	47.8	32.9	63.1	36.0	22.8	57.0
	PII(M4)	46	31	67.4	52.0	80.5	64.0	40.4	101.4
	PII(M10)	70	59	84.3	73.6	91.9	137.7	94.0	201.8
HRV_5.2	PRE	75	0	0.0	0.0	4.8	<20	-	-
	PI(M2)	38	13	34.2	19.6	51.4	20.0	14.1	28.4
	PII(M4)	40	20	50.0	33.8	66.2	34.1	21.9	53.0
	PII(M10)	70	50	71.4	59.4	81.6	78.0	53.1	114.7
HRV_5.8	PRE	71	0	0.0	0.0	5.1	<20	-	-
	PI(M2	36	23	63.9	46.2	79.2	72.8	39.1	135.3
	PII(M4)	34	24	70.6	52.5	84.9	96.3	53.3	174.0
	PII(M10)	59	49	83.1	71.0	91.6	100.7	69.3	146.4
Pooled HRV groups	PRE	222	0	0.0	0.0	1.6	<20	-	-
	PI(M2)	120	58	48.3	39.1	57.6	36.9	27.7	49.2
	PII(M4)	120	75	62.5	53.2	71.2	58.3	43.8	77.5
	PII(M10)	199	158	79.4	73.1	84.8	102.8	82.5	128.0
Placebo	PRE	64	0	0.0	0.0	5.6	<20	-	-
	PI(M2)	38	0	0.0	0.0	9.3	<20	-	-
	PII(M4)	34	0	0.0	0.0	10.3	<20	-	-
	PII(M10)	61	26	42.6	30.0	55.9	49.5	29.4	83.2

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = two months after the Dose 1
PII(M 4) = two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 104: Anti-rotavirus IgA antibody GMC and seroconversion rates in Venezuela (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	180	0	0.0	0.0	2.0	<20	-	-
	PI(M2)	43	14	32.6	19.1	48.5	20.6	14.7	28.9
	PII(M4)	43	26	60.5	44.4	75.0	56.6	32.8	97.7
	PII(M10)	176	134	76.1	69.1	82.2	75.1	59.8	94.4
HRV_5.2	PRE	185	0	0.0	0.0	2.0	<20	-	-
	PI(M2)	43	17	39.5	25.0	55.6	23.1	16.0	33.5
	PII(M4)	46	29	63.0	47.5	76.8	49.7	31.9	77.4
	PII(M10)	179	140	78.2	71.4	84.0	82.9	66.5	103.5
HRV_5.8	PRE	186	0	0.0	0.0	2.0	<20	-	-
	PI(M2)	50	16	32.0	19.5	46.7	22.1	15.6	31.4
	PII(M4)	46	29	63.0	47.5	76.8	68.9	38.8	122.2
	PII(M10)	176	144	81.8	75.3	87.2	83.2	67.8	102.2
Pooled HRV groups	PRE	551	0	0.0	0.0	0.7	<20	-	-
	PI(M2)	136	47	34.6	26.6	43.2	21.9	18.0	26.8
	PII(M4)	135	84	62.2	53.5	70.4	57.9	43.1	77.8
	PII(M10)	531	418	78.7	75.0	82.1	80.4	70.9	91.1
Placebo	PRE	188	0	0.0	0.0	1.9	<20	-	-
	PI(M2)	52	0	0.0	0.0	6.8	<20	-	-
	PII(M4)	51	2	3.9	0.5	13.5	<20	-	-
	PII(M10)	187	83	44.4	37.1	51.8	43.7	33.4	57.1

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = two months after the Dose 1
PII(M 4) = two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 105: Anti-rotavirus IgA antibody GMC and seroconversion rates (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	534	8	1.5	0.6	2.9	<20.0	-	-
	PI(M2)	187	74	39.6	32.5	47.0	28.2	22.8	35.0
	PII(M4)	180	110	61.1	53.6	68.3	53.6	42.0	68.3
	PII(M10)	472	343	72.7	68.4	76.6	79.9	68.8	92.8
HRV_5.2	PRE	529	8	1.5	0.7	3.0	<20.0	-	-
	PI(M2)	174	74	42.5	35.1	50.2	28.1	22.8	34.7
	PII(M4)	166	107	64.5	56.7	71.7	58.8	45.8	75.4
	PII(M10)	463	361	78.0	73.9	81.7	90.4	78.3	104.3
HRV_5.8	PRE	529	13	2.5	1.3	4.2	<20.0	-	-
	PI(M2)	184	80	43.5	36.2	51.0	31.4	25.3	38.9
	PII(M4)	173	117	67.6	60.1	74.5	67.9	53.1	86.9
	PII(M10)	459	356	77.6	73.5	81.3	88.6	76.7	102.3
Placebo	PRE	528	11	2.1	1.0	3.7	<20.0	-	-
	PI(M2)	192	13	6.8	3.7	11.3	<20.0	-	-
	PII(M4)	182	24	13.2	8.6	19.0	<20.0	-	-
	PII(M10)	488	236	48.4	43.8	52.9	53.0	44.6	62.9

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = blood sample taken at two months after Dose 1
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 106: Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing		GMC		
			Value	95% CI	
		N		LL	UL
HRV_4.7	PRE	8	112.3	39.0	323.4
	PI(M2)	74	137.9	104.8	181.4
	PII(M4)	110	155.9	123.7	196.4
	PII(M10)	343	174.6	153.2	198.9
HRV_5.2	PRE	8	139.8	34.2	572.0
	PI(M2)	74	113.9	87.8	147.7
	PII(M4)	107	156.1	124.3	196.1
	PII(M10)	361	168.3	148.8	190.3
HRV_5.8	PRE	13	134.3	59.5	303.2
	PI(M2)	80	138.5	109.0	176.0
	PII(M4)	117	170.0	137.0	210.8
	PII(M10)	356	166.4	147.1	188.4
Placebo	PRE	11	282.5	101.5	786.8
	PI(M2)	13	299.4	132.5	676.7
	PII(M4)	24	287.2	154.4	534.3
	PII(M10)	236	314.2	268.4	367.9

Notes: N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = blood sample taken at two months at two months after Dose 1
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 107: Anti-rotavirus IgA antibody GMC and seroconversion rates in Brazil (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	193	1	0.5	0.0	2.9	<20	-	-
	PI(M2)	73	29	39.7	28.5	51.9	30.8	20.9	45.4
	PII(M4)	67	37	55.2	42.6	67.4	46.1	30.7	69.4
	PII(M10)	177	113	63.8	56.3	70.9	65.8	50.6	85.6
HRV_5.2	PRE	192	0	0.0	0.0	1.9	<20	-	-
	PI(M2)	71	31	43.7	31.9	56.0	31.0	21.9	44.0
	PII(M4)	62	45	72.6	59.8	83.1	73.3	49.9	107.8
	PII(M10)	171	133	77.8	70.8	83.8	98.9	76.8	127.5
HRV_5.8	PRE	191	1	0.5	0.0	2.9	<20	-	-
	PI(M2)	74	31	41.9	30.5	53.9	28.6	20.7	39.5
	PII(M4)	69	44	63.8	51.3	75.0	55.4	38.5	79.7
	PII(M10)	175	122	69.7	62.3	76.4	84.5	65.1	109.8
Pooled HRV groups	PRE	576	2	0.3	0.0	1.2	<20	-	-
	PI(M2)	218	91	41.7	35.1	48.6	30.1	24.6	36.8
	PII(M4)	198	126	63.6	56.5	70.3	56.9	45.6	70.9
	PII(M10)	523	368	70.4	66.2	74.2	81.8	70.4	95.0
Placebo	PRE	192	4	2.1	0.6	5.2	<20	-	-
	PI(M2)	75	9	12.0	5.6	21.6	<20	-	-
	PII(M4)	70	14	20.0	11.4	31.3	<20	-	-
	PII(M10)	179	75	41.9	34.6	49.5	46.2	34.5	61.9

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = two months after the Dose 1
PII(M 4) = two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 108: Anti-rotavirus IgA antibody GMC and seroconversion rates in Mexico (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	99	5	5.1	1.7	11.4	<20	-	-
	PI(M2)	53	27	50.9	36.8	64.9	37.8	24.9	57.5
	PII(M4)	52	36	69.2	54.9	81.3	70.5	45.3	109.7
	PII(M10)	83	71	85.5	76.1	92.3	139.4	99.2	195.9
HRV_5.2	PRE	97	3	3.1	0.6	8.8	<20	-	-
	PI(M2)	50	20	40.0	26.4	54.8	24.9	17.2	36.3
	PII(M4)	52	30	57.7	43.2	71.3	52.8	31.7	88.2
	PII(M10)	86	65	75.6	65.1	84.2	88.0	62.8	123.5
HRV_5.8	PRE	97	4	4.1	1.1	10.2	<20	-	-
	PI(M2)	51	31	60.8	46.1	74.2	57.4	35.1	93.9
	PII(M4)	49	37	75.5	61.1	86.7	98.0	61.9	155.0
	PII(M10)	79	66	83.5	73.5	90.9	96.7	70.9	131.7
Pooled HRV groups	PRE	293	12	4.1	2.1	7.0	<20	-	-
	PI(M2)	154	78	50.6	42.5	58.8	37.9	29.6	48.7
	PII(M4)	153	103	67.3	59.3	74.7	71.0	54.2	93.0
	PII(M10)	248	202	81.5	76.0	86.1	105.8	87.5	127.9
Placebo	PRE	97	5	5.2	1.7	11.6	<20	-	-
	PI(M2)	56	3	5.4	1.1	14.9	<20	-	-
	PII(M4)	52	6	11.5	4.4	23.4	<20	-	-
	PII(M10)	85	46	54.1	43.0	65.0	67.8	44.6	103.1

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = two months after the Dose 1
PII(M 4) = two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 109: Anti-rotavirus IgA antibody GMC and seroconversion rates in Venezuela (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	242	2	0.8	0.1	3.0	<20	-	-
	PI(M2)	61	18	29.5	18.5	42.6	<20	14.7	26.5
	PII(M4)	61	37	60.7	47.3	72.9	50.0	32.6	76.6
	PII(M10)	212	159	75.0	68.6	80.7	75.5	61.4	93.0
HRV_5.2	PRE	240	5	2.1	0.7	4.8	<20	-	-
	PI(M2)	53	23	43.4	29.8	57.7	27.6	18.7	41.0
	PII(M4)	52	32	61.5	47.0	74.7	50.2	32.8	76.9
	PII(M10)	206	163	79.1	72.9	84.5	84.8	69.2	103.9
HRV_5.8	PRE	241	8	3.3	1.4	6.4	<20	-	-
	PI(M2)	59	18	30.5	19.2	43.9	20.9	15.4	28.4
	PII(M4)	55	36	65.5	51.4	77.8	63.3	38.8	103.1
	PII(M10)	205	168	82.0	76.0	87.0	89.1	72.7	109.2
Pooled HRV groups	PRE	723	15	2.1	1.2	3.4	<20	-	-
	PI(M2)	173	59	34.1	27.1	41.7	22.3	18.5	26.9
	PII(M4)	168	105	62.5	54.7	69.8	54.1	41.9	69.7
	PII(M10)	623	490	78.7	75.2	81.8	82.8	73.6	93.2
Placebo	PRE	239	2	0.8	0.1	3.0	<20	-	-
	PI(M2)	61	1	1.6	0.0	8.8	<20	-	-
	PII(M4)	60	4	6.7	1.8	16.2	<20	-	-
	PII(M10)	224	115	51.3	44.6	58.1	53.8	42.1	68.8

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = two months after the Dose 1
PII(M 4) = two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 110: Anti-rotavirus IgA antibody GMC and seroconversion rates for the stool subset (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	154	6	3.9	1.4	8.3	<20.0	-	-
	PI(M2)	134	56	41.8	33.3	50.6	30.9	23.8	40.1
	PII(M4)	135	83	61.5	52.7	69.7	56.2	42.2	74.9
	PII(M10)	136	103	75.7	67.6	82.7	100.9	75.6	134.8
HRV_5.2	PRE	150	3	2.0	0.4	5.7	<20.0	-	-
	PI(M2)	127	52	40.9	32.3	50.0	25.9	20.5	32.7
	PII(M4)	126	81	64.3	55.3	72.6	62.7	46.5	84.5
	PII(M10)	127	91	71.7	63.0	79.3	77.6	58.1	103.5
HRV_5.8	PRE	148	2	1.4	0.2	4.8	<20.0	-	-
	PI(M2)	136	58	42.6	34.2	51.4	31.0	24.0	40.1
	PII(M4)	131	87	66.4	57.6	74.4	64.9	48.8	86.3
	PII(M10)	126	94	74.6	66.1	81.9	88.1	66.4	116.8
Placebo	PRE	149	3	2.0	0.4	5.8	<20.0	-	-
	PI(M2)	144	5	3.5	1.1	7.9	<20.0	-	-
	PII(M4)	138	16	11.6	6.8	18.1	<20.0	-	-
	PII(M10)	134	65	48.5	39.8	57.3	54.9	39.4	76.4

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = blood sample taken at two months after Dose 1
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 111: Percentage of subjects with rotavirus in stool samples collected at pre-determined time points (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Shedding Dose 1								
	Day 0 [Day –1 to Day 0]			[Day 1 to Day 5]			Day 7 [Day 6 to Day 10]		
	N	n	%	N	n	%	N	n	%
HRV-10$^{4.7}$	144	0	0.0	1	0	0.0	136	45	33.1
HRV-10$^{5.2}$	139	0	0.0	1	0	0.0	135	47	34.8
HRV-10$^{5.8}$	136	1	0.7	5	1	20.0	136	59	43.4
Placebo	137	0	0.0	3	0	0.0	135	1	0.7

Group	Shedding Dose 1					
	[Day 11 to Day 12]			Day 60 [Day –6 to Day o of Dose 2]		
	N	n	%	N	n	%
HRV-10$^{4.7}$	1	1	100.0	130	0	0.0
HRV-10$^{5.2}$	2	1	50.0	118	1	0.8
HRV-10$^{5.8}$	2	0	0.0	124	1	0.8
Placebo	0	-	-	132	2	1.5

Group	Shedding Dose 2								
	[Day 1 to Day 5]			Day 7 [Day 6 to Day 10]			[Day 11 to Day 16]		
	N	n	%	N	n	%	N	n	%
HRV-10$^{4.7}$	6	0	0.0	117	15	12.8	5	0	0.0
HRV-10$^{5.2}$	4	1	25.0	118	24	20.3	3	0	0.0
HRV-10$^{5.8}$	7	1	14.3	123	22	17.9	6	0	0.0
Placebo	3	0	0.0	127	1	0.8	4	0	0.0

Notes: N = number of subject with available stool results at the specified time point
n/% = number/percentage of subjects with rotavirus in stool collected at the specified time point

Supplement 112: Percentage of subjects with rotavirus in stool samples collected at pre-determined time points, on combined time points (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Shedding – Combined timepoints				
	N	n	%	95%CI L.L.	U.L.
HRV-10$^{4.7}$	154	57	37.0	29.4	45.2
HRV-10$^{5.2}$	154	68	44.2	36.2	52.4
HRV-10$^{5.8}$	154	75	48.7	40.6	56.9
Placebo	155	4	2.6	0.7	6.5

Notes: N = number of subject with available stool results for at least one time point
n/% = number/percentage of subjects with rotavirus in at least one stool
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 113: Difference between pooled/each HRV vaccine groups and the placebo group in anti-diphtheria antibody seroprotection rates, at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Diphtheria seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	133	70.7	HRV _4.7	146	64.4	Placebo minus HRV _4.7	6.3	-4.7	17.1
			HRV _5.2	136	58.8	Placebo minus HRV _5.2	11.9	0.4	23.0
			HRV _5.8	130	75.4	Placebo minus HRV _5.8	-4.7	-15.4	6.1
			Pooled HRV Groups	412	66.0	Placebo minus Pooled HRV Groups	4.7	-4.7	13.2

Notes: N = number of subjects with available results
% = percentage of subjects with anti-diphtheria antibody concentrations ≥ 0.1 IU/ml (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 114: Difference between pooled/each HRV vaccine groups and the placebo group in anti-diphtheria antibody seroprotection rates, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Diphtheria seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	149	74.5	HRV _4.7	164	70.1	Placebo minus HRV _4.7	4.4	-5.6	14.2
			HRV _5.2	149	68.5	Placebo minus HRV _5.2	6.0	-4.2	16.2
			HRV _5.8	142	70.4	Placebo minus HRV _5.8	4.1	-6.2	14.3
			Pooled HRV Groups	455	69.7	Placebo minus Pooled HRV Groups	4.8	-3.7	12.6

Notes: N = number of subjects with available results
% = percentage of subjects with anti-diphtheria antibody concentrations ≥ 0.1 IU/ml (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 115: Ratio of anti-diphtheria antibody GMCs between pooled/each HRV vaccine groups and the placebo group, at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	133	0.3	HRV _4.7	146	0.2	Placebo over HRV _4.7	1.36	0.99	1.86
			HRV _5.2	136	0.2	Placebo over HRV _5.2	1.51	1.10	2.08
			HRV _5.8	130	0.2	Placebo over HRV _5.8	1.12	0.81	1.55
						Placebo over Pooled HRV Groups*	1.32	1.02	1.72

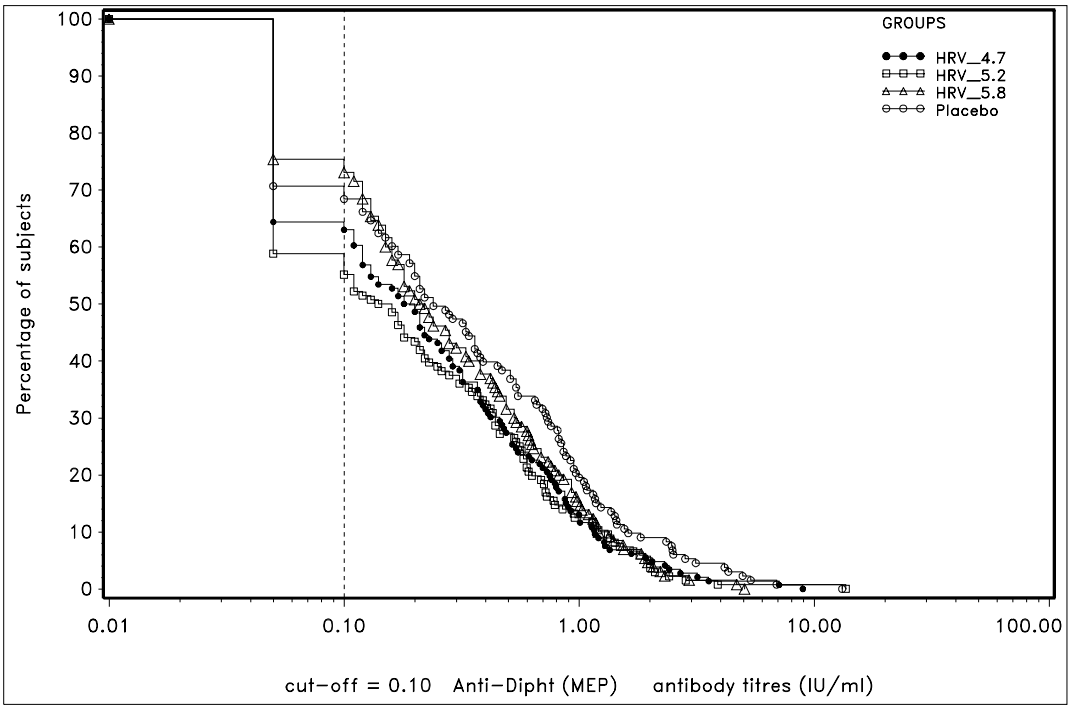
Notes: N = number of subjects with available data
95%CI, LL, UL = 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 116: Ratio of anti-diphtheria antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

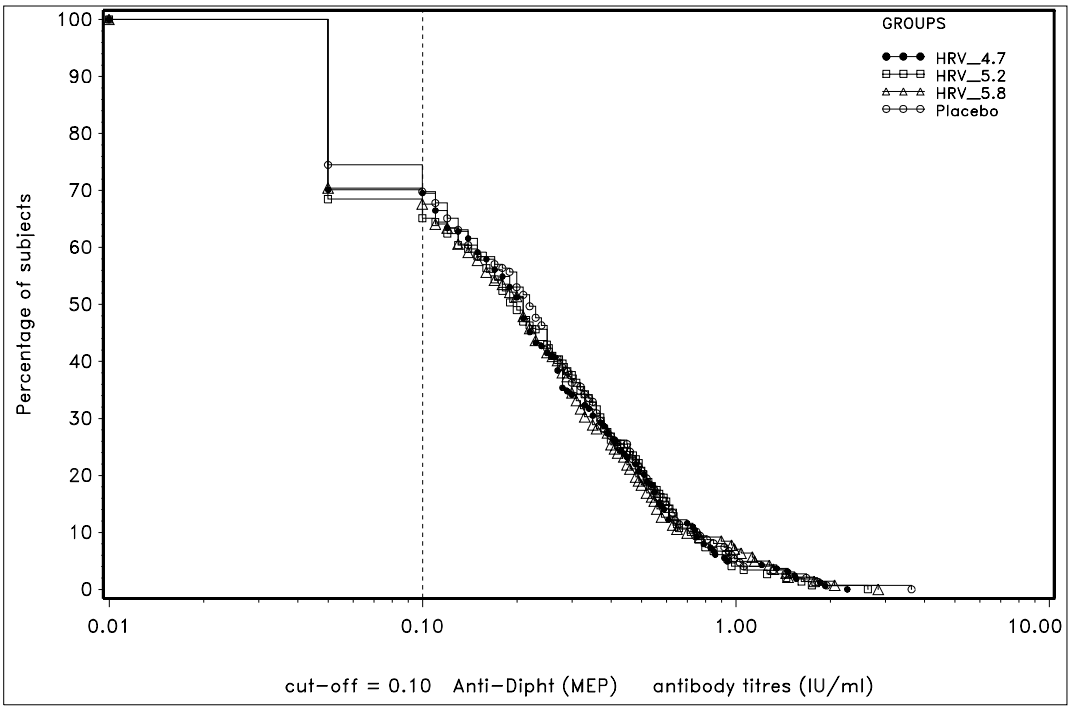
						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	149	0.2	HRV _4.7	164	0.2	Placebo over HRV _4.7	1.06	0.84	1.35
			HRV _5.2	149	0.2	Placebo over HRV _5.2	1.08	0.85	1.38
			HRV _5.8	142	0.2	Placebo over HRV _5.8	1.07	0.84	1.37
						Placebo over Pooled HRV Groups*	1.07	0.88	1.31

Notes: N = number of subjects with available data
95%CI, LL, UL = 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 117: Reverse cumulative curve for anti-diphtheria antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 118: Reverse cumulative curve for anti-diphtheria antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 119: Difference between pooled/each HRV vaccine groups and the placebo group in anti-tetanus antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Tetanus seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	134	99.3	HRV _4.7	147	98.6	Placebo minus HRV _4.7	0.6	-2.9	4.2
			HRV _5.2	136	100.0	Placebo minus HRV _5.2	-0.7	-4.1	2.0
			HRV _5.8	131	97.7	Placebo minus HRV _5.8	1.5	-2.0	5.9
			Pooled HRV Groups	414	98.8	Placebo minus Pooled HRV Groups	0.5	-2.9	2.2

Notes: N = number of subjects with available results
% = percentage of subjects with anti-tetanus antibody concentrations ≥ 0.1 IU/ml (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 120: Difference between pooled/each HRV vaccine groups and the placebo group in anti-tetanus antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Tetanus seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	149	100.0	HRV _4.7	166	100.0	Placebo minus HRV _4.7	0.0	-2.5	2.3
			HRV _5.2	150	98.7	Placebo minus HRV _5.2	1.3	-1.2	4.7
			HRV _5.8	143	100.0	Placebo minus HRV _5.8	0.0	-2.5	2.6
			Pooled HRV Groups	459	99.6	Placebo minus Pooled HRV Groups	0.4	-2.1	1.6

Notes: N = number of subjects with available results
% = percentage of subjects with anti-tetanus antibody concentrations ≥ 0.1 IU/ml (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 121: Ratio of anti-tetanus antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	N	GMC	Group	N	GMC	GMC ratio Groups	Value %	95% CI LL	UL
Placebo	134	1.2	HRV _4.7	147	1.1	Placebo over HRV _4.7	1.05	0.81	1.35
			HRV _5.2	136	1.1	Placebo over HRV _5.2	1.06	0.82	1.37
			HRV _5.8	131	1.1	Placebo over HRV _5.8	1.10	0.85	1.43
						Placebo over Pooled HRV Groups*	1.07	0.87	1.32

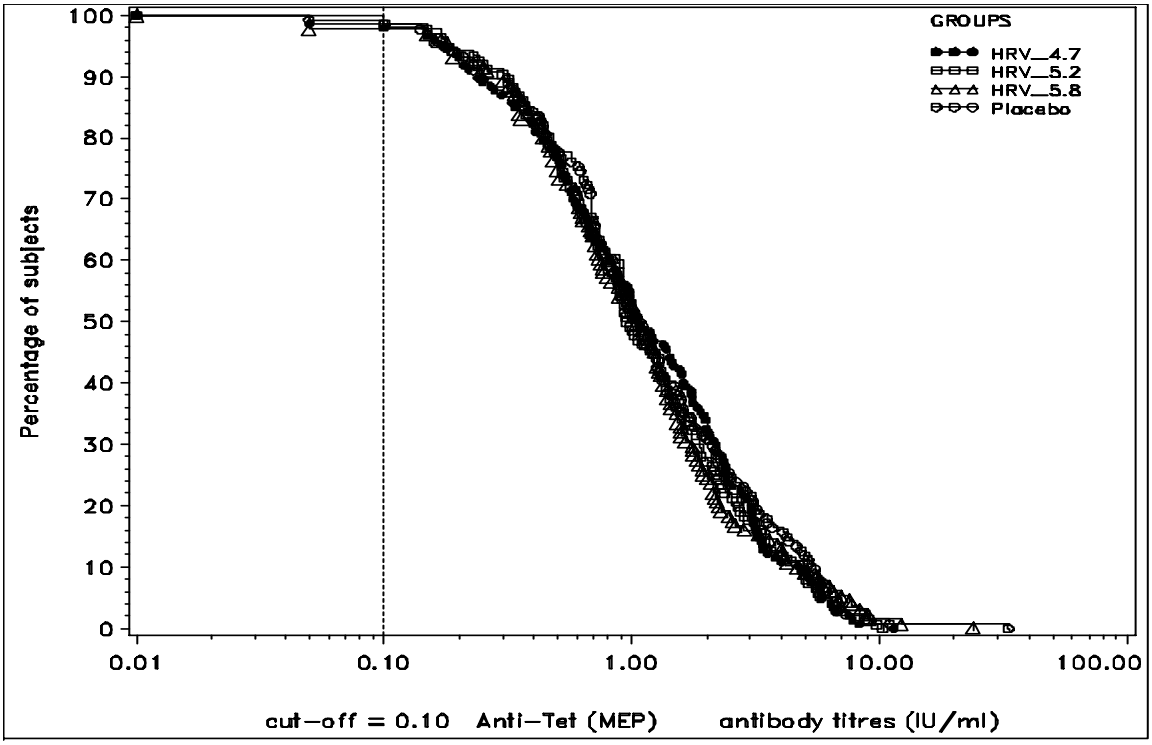
Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 122: Ratio of anti-tetanus antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

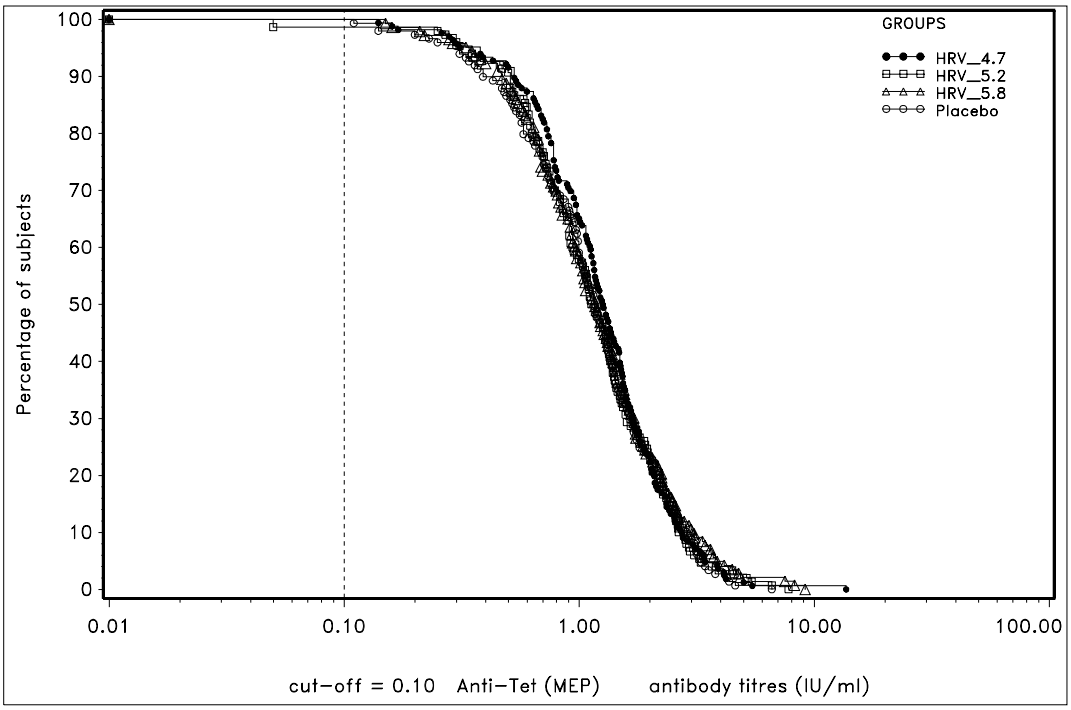
Group	N	GMC	Group	N	GMC	GMC ratio Groups	Value %	95% CI LL	UL
Placebo	149	1.1	HRV _4.7	166	1.2	Placebo over HRV _4.7	0.91	0.77	1.07
			HRV _5.2	150	1.1	Placebo over HRV _5.2	0.98	0.83	1.16
			HRV _5.8	143	1.2	Placebo over HRV _5.8	0.95	0.80	1.13
						Placebo over Pooled HRV Groups*	0.95	0.83	1.09

Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 123: Reverse cumulative curve for anti-tetanus antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 124: Reverse cumulative curve for anti-tetanus antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 125: Difference between pooled/each HRV vaccine groups and the placebo group in anti-BPT antibody seropositivity rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-BPT seropositivity			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	130	61.5	HRV _4.7	144	65.3	Placebo minus HRV _4.7	-3.7	-15.1	7.6
			HRV _5.2	134	59.0	Placebo minus HRV _5.2	2.6	-9.2	14.3
			HRV _5.8	131	64.1	Placebo minus HRV _5.8	-2.6	-14.2	9.1
			Pooled HRV Groups	409	62.8	Placebo minus Pooled HRV Groups	-1.3	-11.0	8.0

Notes: N = number of subjects with available results
% = percentage of subjects with anti-BPT antibody concentrations ≥ 15 EL.U/ml (seropositivity)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 126: Difference between pooled/each HRV vaccine groups and the placebo group in anti-BPT seropositivity rates at the end of the first efficacy period (ATP cohort for immunogenicity)

						Difference in anti-BPT seropositivity			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	148	71.6	HRV _4.7	165	75.2	Placebo minus HRV _4.7	-3.5	-13.4	6.2
			HRV _5.2	151	80.1	Placebo minus HRV _5.2	-8.5	-18.2	1.2
			HRV _5.8	144	70.1	Placebo minus HRV _5.8	1.5	-8.9	11.9
			Pooled HRV Groups	460	75.2	Placebo minus Pooled HRV Groups	-3.6	-12.2	4.3

Notes: N = number of subjects with available results
% = percentage of subjects with anti-BPT antibody concentrations ≥ 15 EL.U/ml (seropositivity)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 127: Ratio of anti-BPT antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	N	GMC	Group	N	GMC	GMC ratio Groups	Value %	95% CI LL	UL
Placebo	130	17.6	HRV _4.7	144	19.4	Placebo over HRV _4.7	0.91	0.75	1.10
			HRV _5.2	134	18.5	Placebo over HRV _5.2	0.95	0.78	1.15
			HRV _5.8	131	18.4	Placebo over HRV _5.8	0.96	0.79	1.16
						Placebo over Pooled HRV Groups*	0.94	0.80	1.10

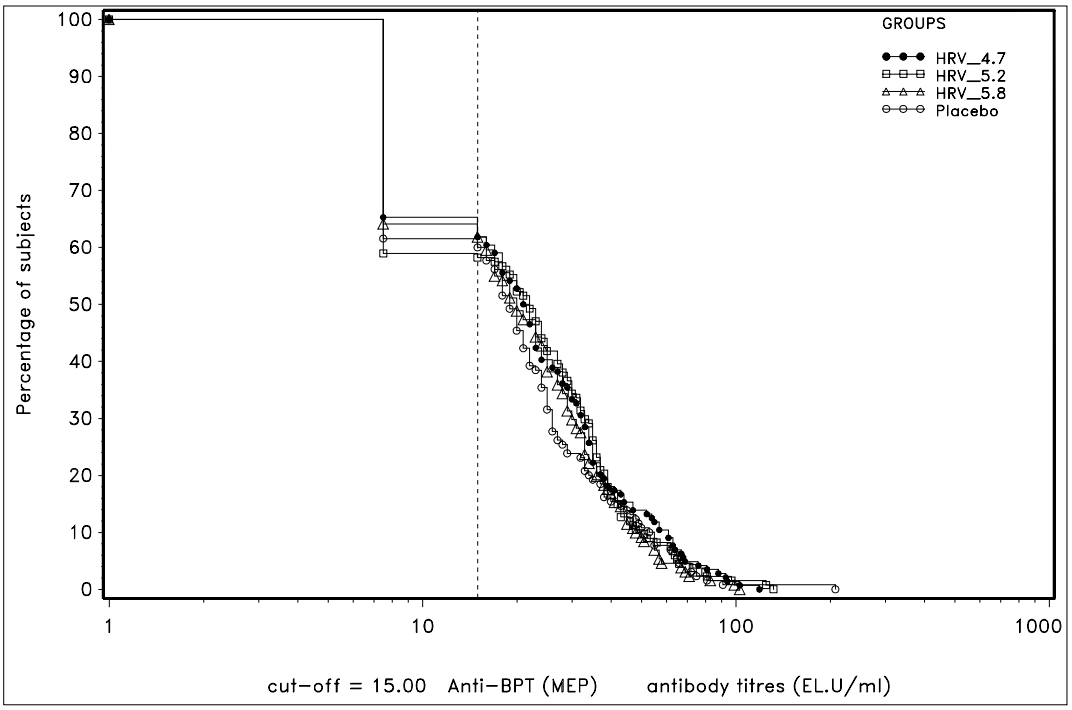
Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 128: Ratio of anti-BPT antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

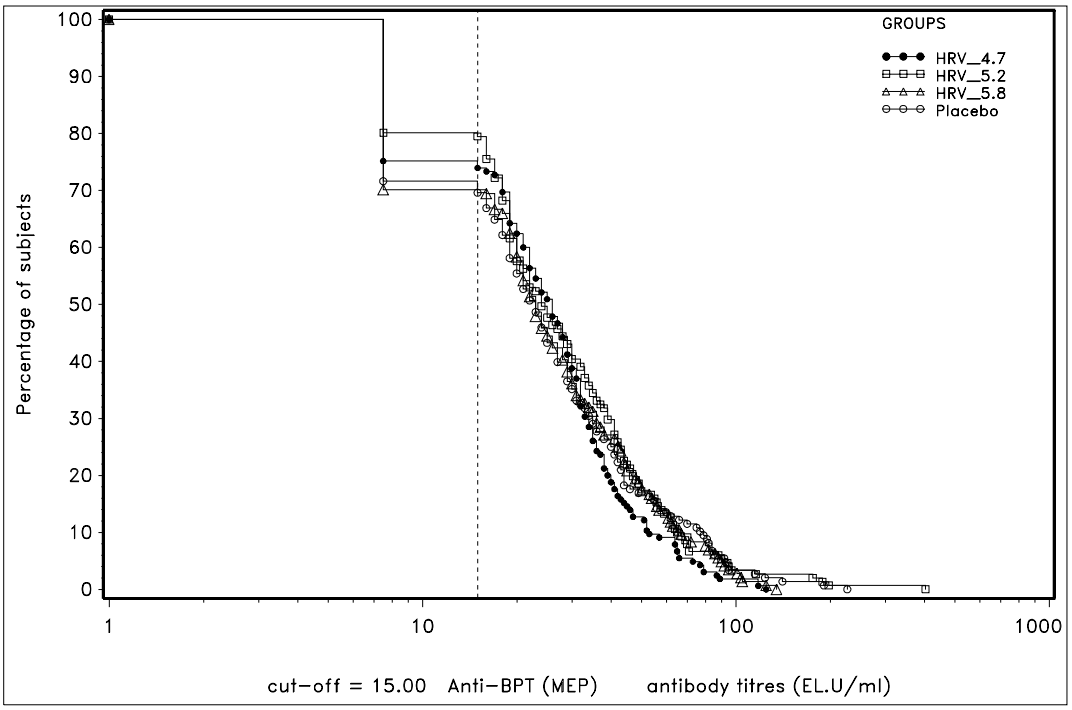
Group	N	GMC	Group	N	GMC	GMC ratio Groups	Value %	95% CI LL	UL
Placebo	148	22.4	HRV _4.7	165	22.5	Placebo over HRV _4.7	0.99	0.83	1.19
			HRV _5.2	151	25.2	Placebo over HRV _5.2	0.89	0.74	1.07
			HRV _5.8	144	22.2	Placebo over HRV _5.8	1.01	0.83	1.21
						Placebo over Pooled HRV Groups*	0.96	0.83	1.12

Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 129: Reverse cumulative curve for anti-BPT antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 130: Reverse cumulative curve for anti-BPT antibody concentrations at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 131: Difference between pooled/each HRV vaccine groups and the placebo group in anti-HBs antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-HBS seroportection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	133	98.5	HRV _4.7	147	98.6	Placebo minus HRV _4.7	-0.1	-4.1	3.5
			HRV _5.2	136	98.5	Placebo minus HRV _5.2	0.0	-4.0	3.9
			HRV _5.8	134	97.0	Placebo minus HRV _5.8	1.5	-2.7	6.1
			Pooled HRV Groups	417	98.1	Placebo minus Pooled HRV Groups	0.4	-3.5	2.6

Notes: N = number of subjects with available results
% = percentage of subjects with anti-HBs antibody concentrations ≥ 10 mIU/ml (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 132: Difference between pooled/each HRV vaccine groups and the placebo group in anti-HBs antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-HBS seroportection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	149	96.6	HRV _4.7	165	95.2	Placebo minus HRV _4.7	1.5	-3.4	6.4
			HRV _5.2	150	96.7	Placebo minus HRV _5.2	0.0	-4.7	4.6
			HRV _5.8	143	97.9	Placebo minus HRV _5.8	-1.3	-5.8	3.0
			Pooled HRV Groups	458	96.5	Placebo minus Pooled HRV Groups	0.1	-4.3	3.0

Notes: N = number of subjects with available results
% = percentage of subjects with anti-HBs antibody concentrations ≥ 10 mIU/ml (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 133: Ratio of anti-HBs antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	N	GMC	Group	N	GMC	GMC ratio Groups	Value %	95% CI LL	UL
Placebo	133	674.9	HRV _4.7	147	550.6	Placebo over HRV _4.7	1.23	0.89	1.69
			HRV _5.2	136	595.7	Placebo over HRV _5.2	1.13	0.82	1.57
			HRV _5.8	134	515.9	Placebo over HRV _5.8	1.31	0.94	1.82
						Placebo over Pooled HRV Groups*	1.22	0.93	1.60

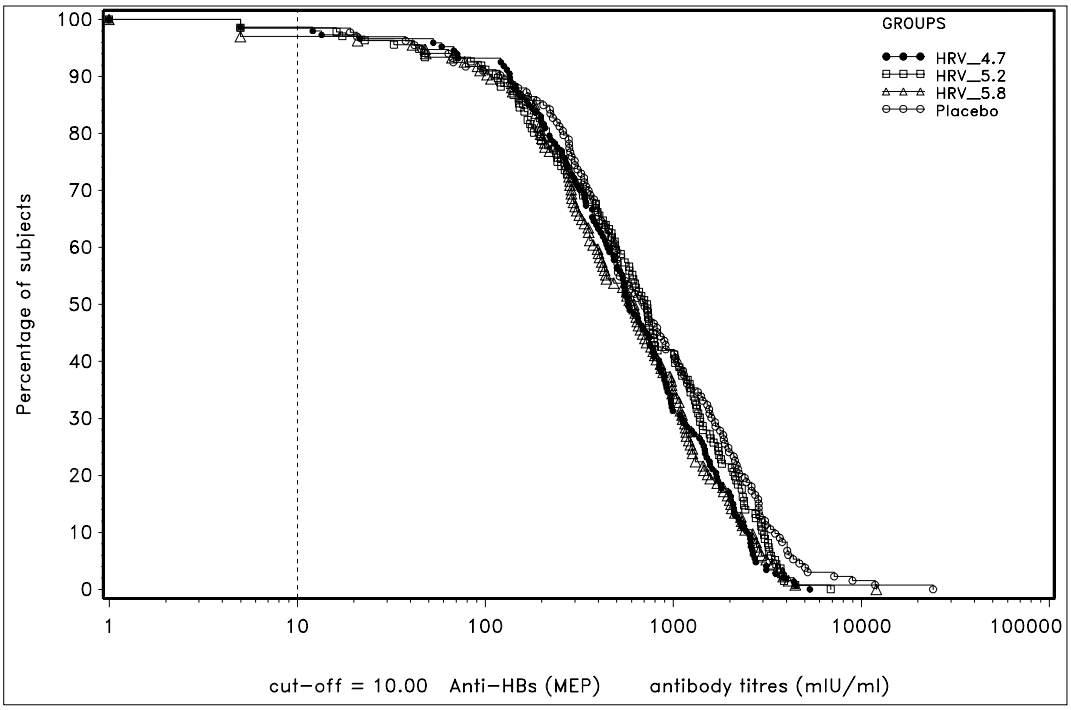
Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 134: Ratio of anti-HBs antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

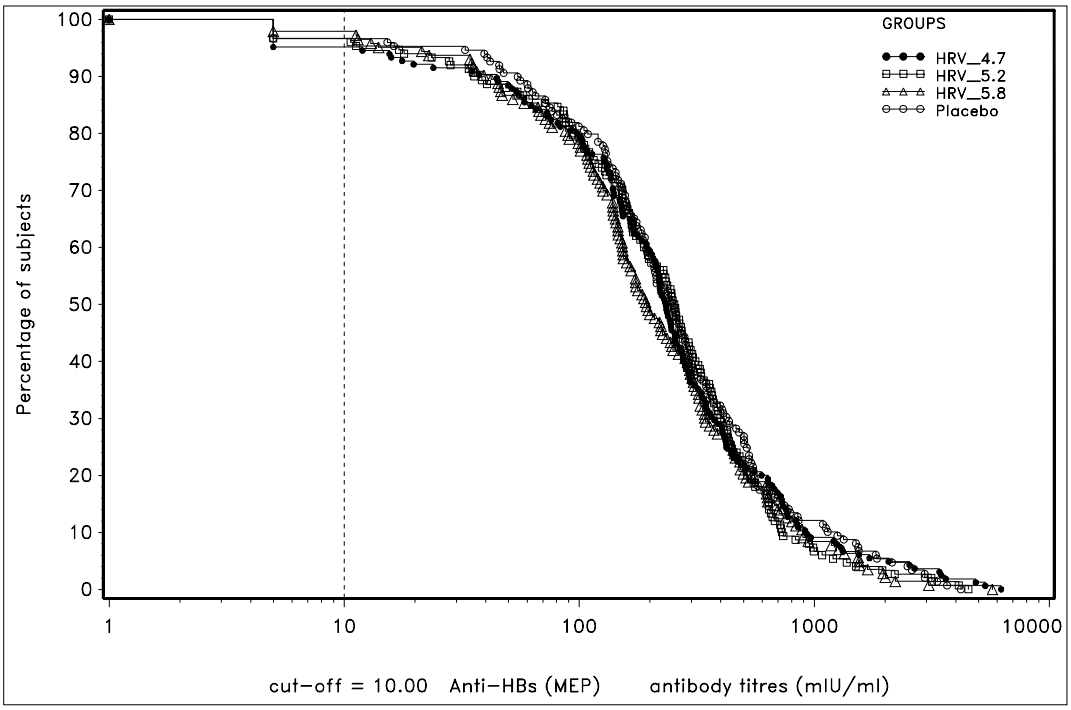
Group	N	GMC	Group	N	GMC	GMC ratio Groups	Value %	95% CI LL	UL
Placebo	149	238.7	HRV _4.7	165	212.7	Placebo over HRV _4.7	1.12	0.84	1.50
			HRV _5.2	150	214.4	Placebo over HRV _5.2	1.11	0.83	1.50
			HRV _5.8	143	200.0	Placebo over HRV _5.8	1.19	0.88	1.62
						Placebo over Pooled HRV Groups*	1.14	0.89	1.46

Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 135: Reverse cumulative curve for anti-HBs antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 136: Reverse cumulative curve for anti-HBs antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 137: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP concentrations ≥ 0.15 mcg/ml at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity)

						Difference in percentage of subjects with anti-PRP concentrations ≥ 0.15 mcg/ml			
							Value	**95% CI**	
Group	**N**	**%**	**Group**	**N**	**%**	**Groups**	**%**	**LL**	**UL**
Placebo	131	99.2	HRV _4.7	143	100.0	Placebo minus HRV _4.7	-0.8	-4.2	1.9
			HRV _5.2	136	99.3	Placebo minus HRV _5.2	0.0	-3.5	3.4
			HRV _5.8	133	99.2	Placebo minus HRV _5.8	0.0	-3.5	3.4
			Pooled HRV Groups	412	99.5	Placebo minus Pooled HRV Groups	-0.3	-3.7	1.1

Notes: N = number of subjects with available results
% = percentage of subjects with anti-PRP antibody concentrations ≥ 0.15 mcg/ml
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 138: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP antibody concentrations ≥ 1 mcg/ml at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in percentage of subjects with anti-PRP concentrations ≥ 1 mcg/ml			
							Value	**95% CI**	
Group	**N**	**%**	**Group**	**N**	**%**	**Groups**	**%**	**LL**	**UL**
Placebo	131	89.3	HRV _4.7	143	96.5	Placebo minus HRV _4.7	-7.2	-14.1	-1.3
			HRV _5.2	136	88.2	Placebo minus HRV _5.2	1.1	-6.8	8.9
			HRV _5.8	133	91.0	Placebo minus HRV _5.8	-1.7	-9.2	5.8
			Pooled HRV Groups	412	92.0	Placebo minus Pooled HRV Groups	-2.7	-9.5	2.5

Notes: N = number of subjects with available results
% = percentage of subjects with anti-PRP antibody concentrations ≥ 1 mcg/ml
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 139: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP antibody concentrations ≥ 0.15 mcg/ml at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in percentage of subjects with anti-PRP concentrations ≥ 0.15 mcg/ml			
Group	**N**	**%**	**Group**	**N**	**%**	**Groups**	**Value %**	**95% CI LL**	**UL**
Placebo	149	100.0	HRV _4.7	165	99.4	Placebo minus HRV _4.7	0.6	-1.9	3.4
			HRV _5.2	149	99.3	Placebo minus HRV _5.2	0.7	-1.9	3.7
			HRV _5.8	143	100.0	Placebo minus HRV _5.8	0.0	-2.5	2.6
			Pooled HRV Groups	457	99.6	Placebo minus Pooled HRV Groups	0.4	-2.1	1.6

Notes: N = number of subjects with available results
% = percentage of subjects with anti-PRP antibody concentrations ≥ 0.15 mcg/ml
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 140: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP antibody concentrations ≥ 1 mcg/ml ml at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in percentage of subjects with anti-PRP concentrations ≥ 1 mcg/ml			
Group	**N**	**%**	**Group**	**N**	**%**	**Groups**	**Value %**	**95% CI LL**	**UL**
Placebo	149	94.6	HRV _4.7	165	93.9	Placebo minus HRV _4.7	0.7	-4.9	6.2
			HRV _5.2	149	91.3	Placebo minus HRV _5.2	3.4	-2.6	9.7
			HRV _5.8	143	91.6	Placebo minus HRV _5.8	3.0	-3.0	9.4
			Pooled HRV Groups	457	92.3	Placebo minus Pooled HRV Groups	2.3	-3.0	6.2

Notes: N = number of subjects with available results
% = percentage of subjects with anti-PRP antibody concentrations ≥ 1 mcg/ml
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 141: Ratio of anti-PRP antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	131	5.1	HRV _4.7	143	6.4	Placebo over HRV _4.7	0.79	0.59	1.06
			HRV _5.2	136	5.6	Placebo over HRV _5.2	0.90	0.67	1.21
			HRV _5.8	133	5.1	Placebo over HRV _5.8	0.99	0.74	1.34
						Placebo over Pooled HRV Groups*	0.89	0.70	1.13

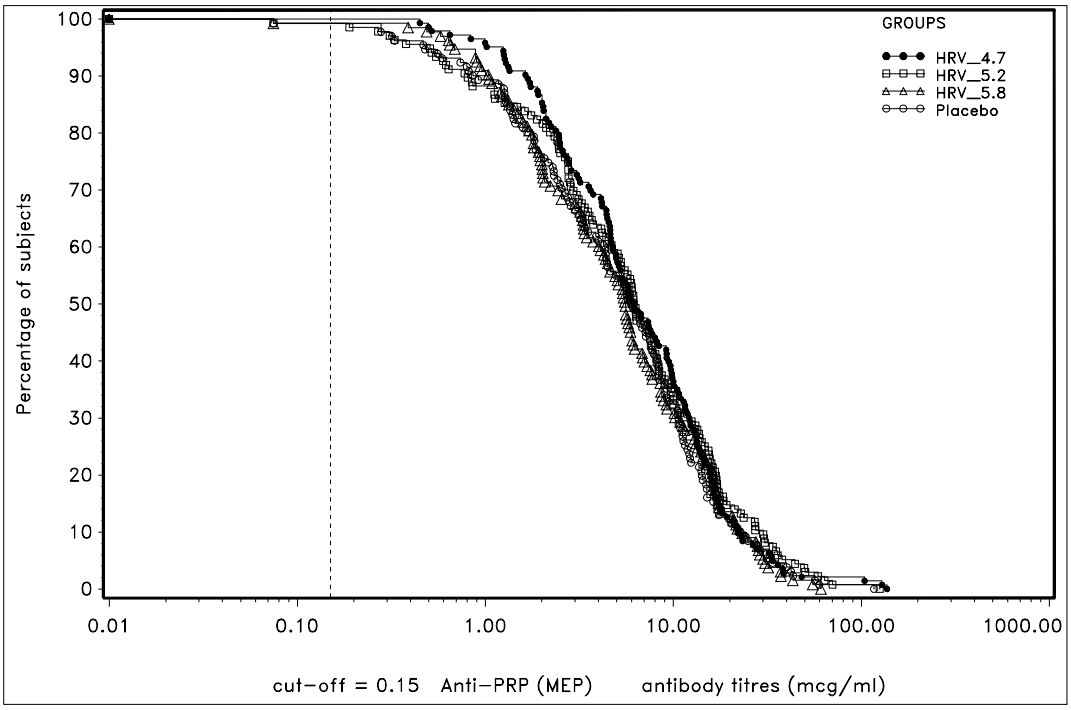
Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
*For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 142: Ratio of anti-PRP antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

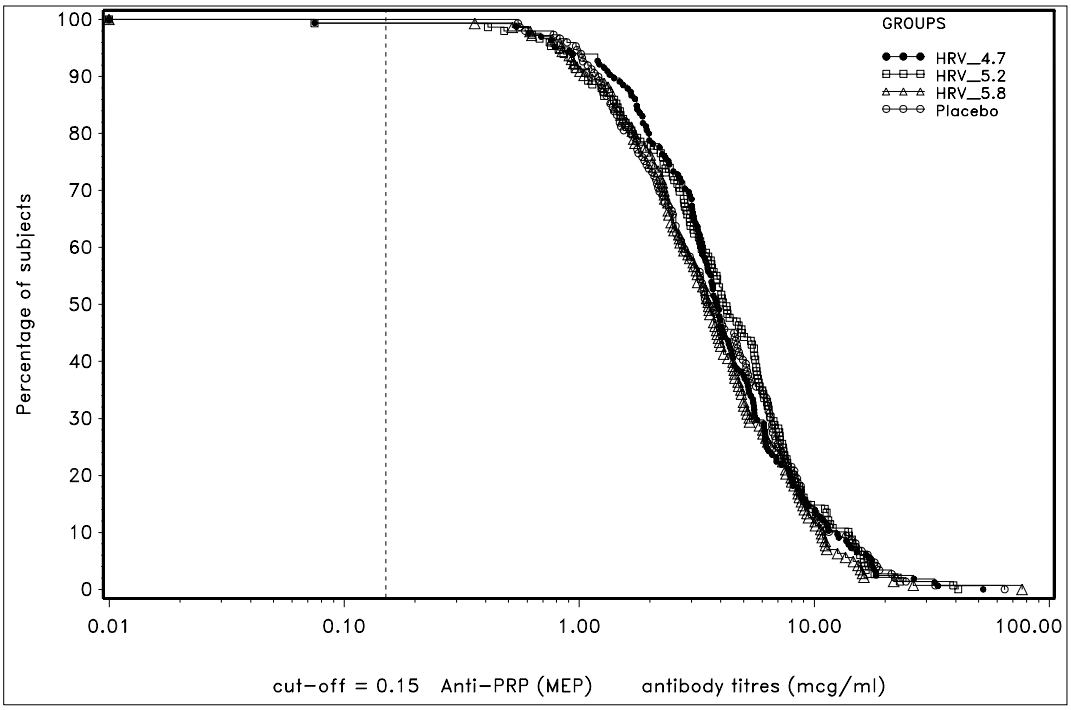
						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	149	3.8	HRV _4.7	165	4.0	Placebo over HRV _4.7	0.96	0.79	1.18
			HRV _5.2	149	4.0	Placebo over HRV _5.2	0.96	0.78	1.18
			HRV _5.8	143	3.6	Placebo over HRV _5.8	1.07	0.87	1.32
						Placebo over Pooled HRV Groups*	0.99	0.84	1.18

Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 143: Reverse cumulative curve for anti-PRP antibody concentrations, at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 144: Reverse cumulative curve for anti-PRP antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 145: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 1 antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Polio 1 seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	130	99.2	HRV _4.7	147	98.6	Placebo minus HRV _4.7	0.6	-3.0	4.1
			HRV _5.2	135	97.8	Placebo minus HRV _5.2	1.5	-2.2	5.7
			HRV _5.8	133	98.5	Placebo minus HRV _5.8	0.7	-2.9	4.6
			Pooled HRV Groups	415	98.3	Placebo minus Pooled HRV Groups	0.9	-2.6	2.8

Notes: N = number of subjects with available results
% = percentage of subjects with anti-poliovirus type 1 antibody titers ≥ 8 ED50 (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 146: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 2 antibody seroprotection at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Polio 2 seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	130	99.2	HRV _4.7	147	98.6	Placebo minus HRV _4.7	0.6	-3.0	4.1
			HRV _5.2	135	99.3	Placebo minus HRV _5.2	0.0	-3.6	3.4
			HRV _5.8	133	99.2	Placebo minus HRV _5.8	0.0	-3.5	3.4
			Pooled HRV Groups	415	99.0	Placebo minus Pooled HRV Groups	0.2	-3.3	1.9

Notes: N = number of subjects with available results
% = percentage of subjects with anti-poliovirus type 2 antibody titers ≥ 8 ED50 (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 147: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 3 antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Polio 3 seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	130	84.6	HRV _4.7	147	87.1	Placebo minus HRV _4.7	-2.5	-11.0	5.8
			HRV _5.2	135	84.4	Placebo minus HRV _5.2	0.2	-8.7	9.0
			HRV _5.8	133	89.5	Placebo minus HRV _5.8	-4.9	-13.3	3.3
			Pooled HRV Groups	415	87.0	Placebo minus Pooled HRV Groups	-2.4	-10.1	4.0

Notes: N = number of subjects with available results
% = percentage of subjects with anti-poliovirus type 3 antibody titers ≥ 8 ED50 (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 148: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 1 antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Polio 1 seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	138	100.0	HRV _4.7	156	99.4	Placebo minus HRV _4.7	0.6	-2.1	3.5
			HRV _5.2	139	100.0	Placebo minus HRV _5.2	0.0	-2.7	2.7
			HRV _5.8	134	100.0	Placebo minus HRV _5.8	0.0	-2.7	2.8
			Pooled HRV Groups	429	99.8	Placebo minus Pooled HRV Groups	0.2	-2.5	1.3

Notes:
N = number of subjects with available results
% = percentage of subjects with anti-poliovirus type 1 antibody titers ≥ 8 ED50 (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 149: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 2 antibody seroprotection at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Polio 2 seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	148	99.3	HRV _4.7	164	98.8	Placebo minus HRV _4.7	0.5	-2.6	3.7
			HRV _5.2	147	100.0	Placebo minus HRV _5.2	-0.7	-3.7	1.9
			HRV _5.8	140	100.0	Placebo minus HRV _5.8	-0.7	-3.7	2.0
			Pooled HRV Groups	451	99.6	Placebo minus Pooled HRV Groups	-0.2	-3.3	1.1

Notes: N = number of subjects with available results
% = percentage of subjects with anti-poliovirus type 2 antibody titers ≥ 8 ED50 (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 150: Difference between pooled/ each HRV vaccine groups and the placebo group in anti-poliovirus type 3 antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Polio 3 seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	148	93.2	HRV _4.7	164	92.1	Placebo minus HRV _4.7	1.2	-5.0	7.2
			HRV _5.2	147	91.2	Placebo minus HRV _5.2	2.1	-4.3	8.6
			HRV _5.8	140	95.0	Placebo minus HRV _5.8	-1.8	-7.7	4.0
			Pooled HRV Groups	451	92.7	Placebo minus Pooled HRV Groups	0.6	-5.0	4.7

Notes: N = number of subjects with available results
% = percentage of subjects with anti-poliovirus type 3 antibody titers ≥ 8 ED50 (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 151: Ratio of anti-poliovirus type 1 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	130	1322.7	HRV _4.7	147	1546.9	Placebo over HRV _4.7	0.86	0.60	1.22
			HRV _5.2	135	1120.1	Placebo over HRV _5.2	1.18	0.82	1.70
			HRV _5.8	133	1261.4	Placebo over HRV _5.8	1.05	0.73	1.51
						Placebo over Pooled HRV Groups*	1.01	0.75	1.36

Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMT ratio is derived as the geometric mean of the 3 individual GMT ratios

Supplement 152: Ratio of anti-poliovirus type 2 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	130	1112.1	HRV _4.7	147	1138.6	Placebo over HRV _4.7	0.98	0.72	1.32
			HRV _5.2	135	1042.7	Placebo over HRV _5.2	1.10	0.78	1.45
			HRV _5.8	133	1346.2	Placebo over HRV _5.8	0.83	0.61	1.12
						Placebo over Pooled HRV Groups*	0.95	0.74	1.23

Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
For the pooled HRV group, the GMT ratio is derived as the geometric mean of the 3 individual GMT ratios

Supplement 153: Ratio of anti-poliovirus type 3 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	130	155.5	HRV _4.7	147	184.1	Placebo over HRV _4.7	0.84	0.55	1.31
			HRV _5.2	135	158.0	Placebo over HRV _5.2	0.98	0.63	1.53
			HRV _5.8	133	181.1	Placebo over HRV _5.8	0.86	0.55	1.34
						Placebo over Pooled HRV Groups*	0.89	0.62	1.28

Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMT ratio is derived as the geometric mean of the 3 individual GMT ratios

Supplement 154: Ratio of anti-poliovirus type 1 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	138	693.9	HRV _4.7	156	802.1	Placebo over HRV _4.7	0.87	0.66	1.14
			HRV _5.2	139	731.3	Placebo over HRV _5.2	0.95	0.71	1.26
			HRV _5.8	134	714.8	Placebo over HRV _5.8	0.97	0.73	1.29
						Placebo over Pooled HRV Groups*	0.92	0.73	1.17

Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMT ratio is derived as the geometric mean of the 3 individual GMT ratios

Supplement 155: Ratio of anti-poliovirus type 2 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	148	438.7	HRV _4.7	164	469.7	Placebo over HRV _4.7	0.93	0.74	1.18
			HRV _5.2	147	472.6	Placebo over HRV _5.2	0.93	0.73	1.18
			HRV _5.8	140	523.6	Placebo over HRV _5.8	0.84	0.66	1.07
						Placebo over Pooled HRV Groups*	0.90	0.74	1.09

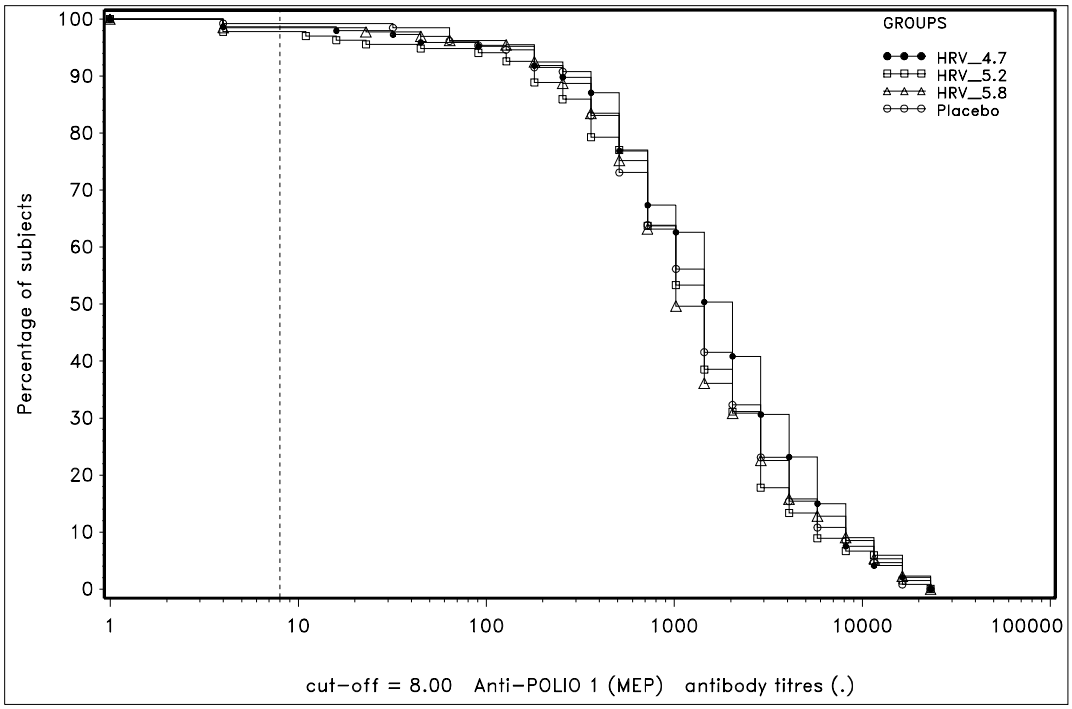
Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMT ratio is derived as the geometric mean of the 3 individual GMT ratios

Supplement 156: Ratio of anti-poliovirus type 3 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

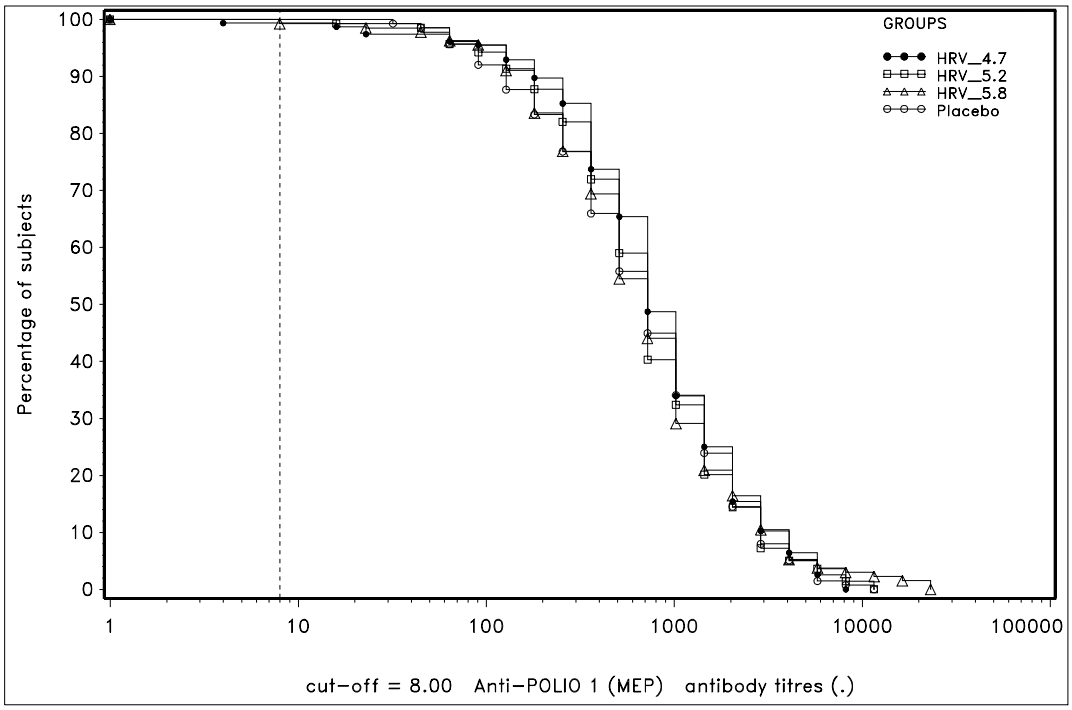
						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	148	109.2	HRV _4.7	164	131.1	Placebo over HRV _4.7	0.83	0.61	1.14
			HRV _5.2	147	107.3	Placebo over HRV _5.2	1.02	0.74	1.40
			HRV _5.8	140	130.9	Placebo over HRV _5.8	0.83	0.60	1.16
						Placebo over Pooled HRV Groups*	0.89	0.68	1.16

Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMT ratio is derived as the geometric mean of the 3 individual GMT ratios

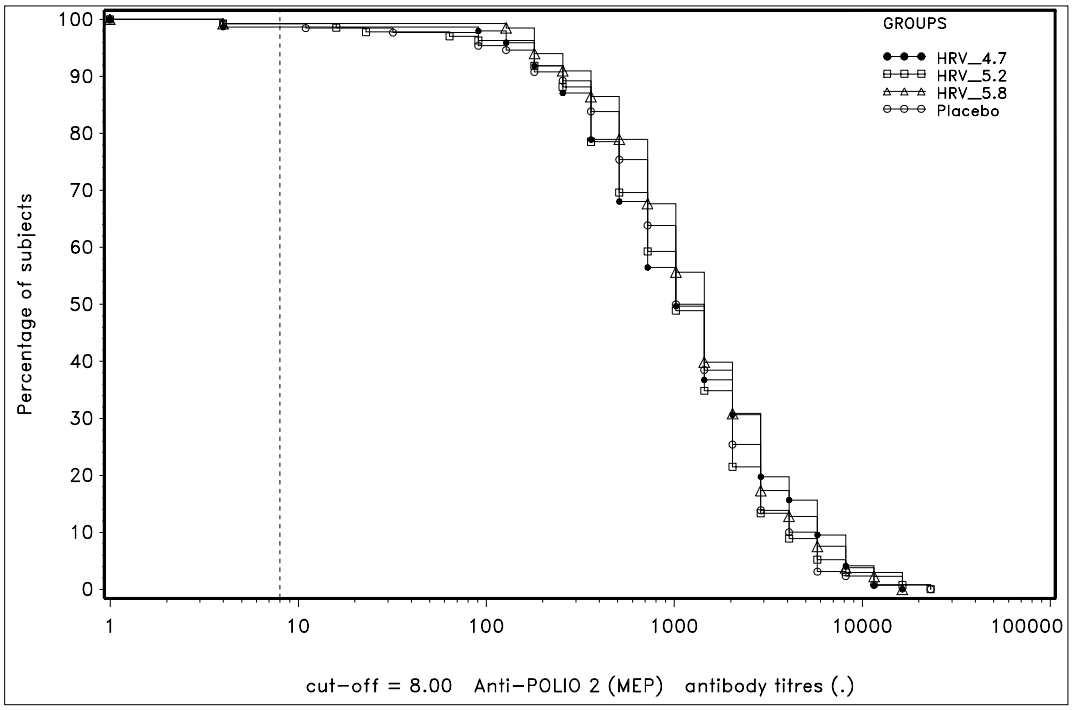
Supplement 157: Reverse cumulative curve for anti-poliovirus type 1 antibody titers at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



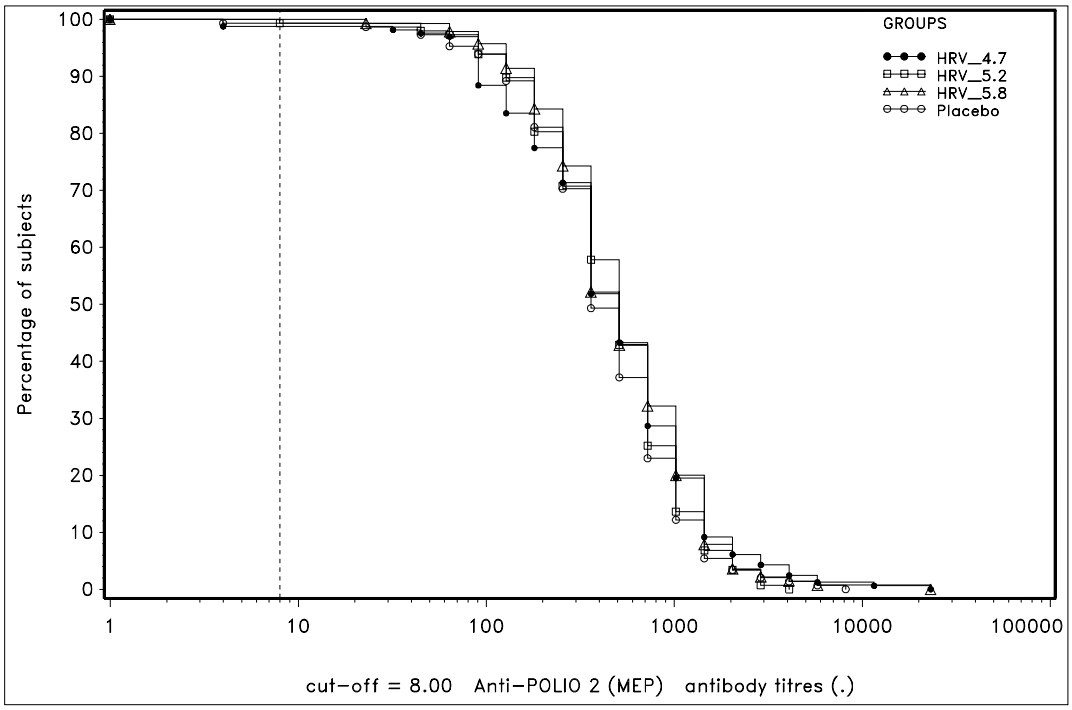
Supplement 158: Reverse cumulative curve for anti-poliovirus type 1 antibody titers at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



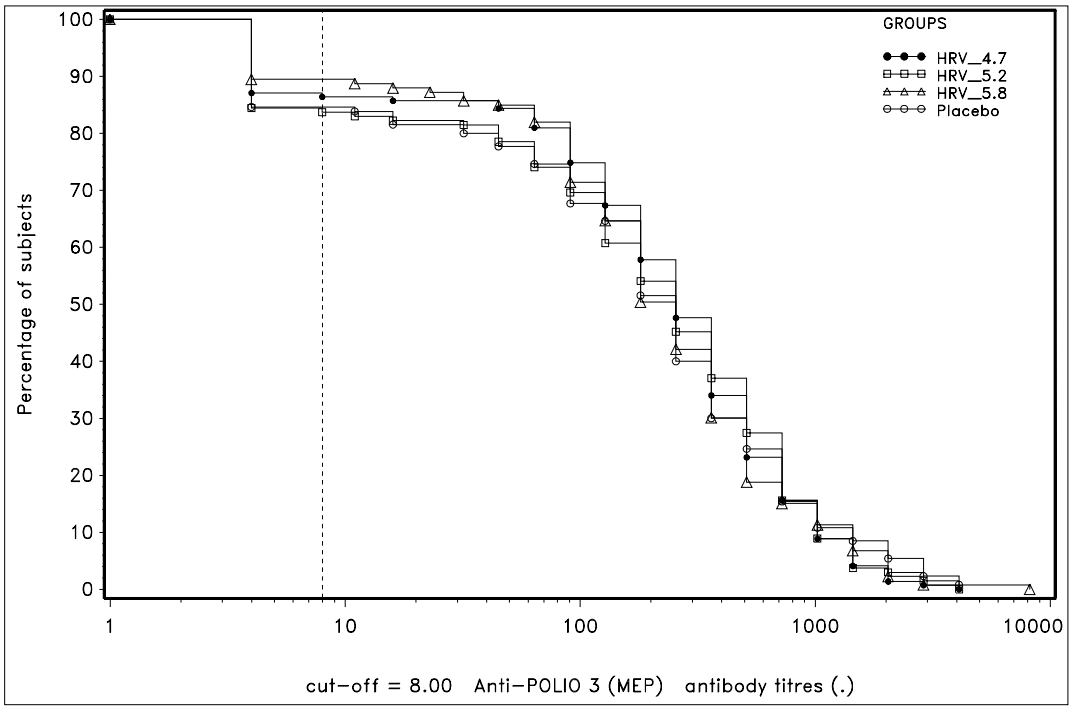
Supplement 159: Reverse cumulative curve for anti-poliovirus type 2 antibody titers at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



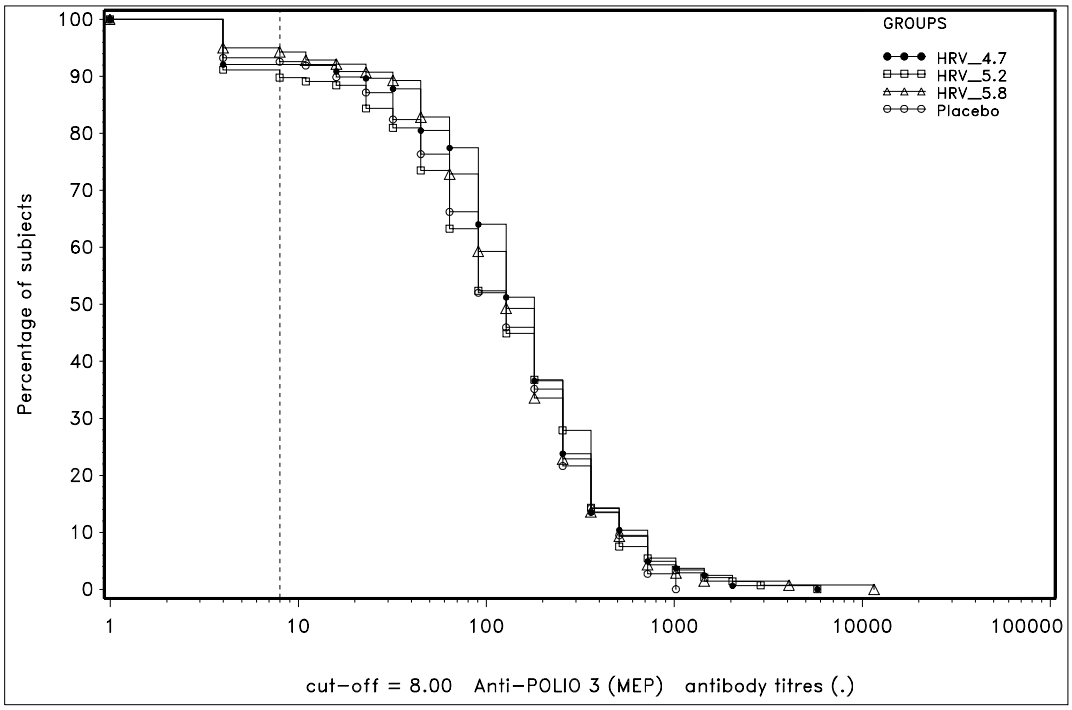
Supplement 160: Reverse cumulative curve for anti-poliovirus type 2 antibody titers at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 161: Reverse cumulative curve for anti-poliovirus type 3 antibody titers at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 162: Reverse cumulative curve for anti-poliovirus type 3 antibody titers at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 163: Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Antibody	Group	Timing	N	≥ 0.1 IU/ml				GMC		
						95% CI		Value	95% CI	
				n	%	LL	UL		LL	UL
Anti-Diphtheria	**HRV_4.7**	PII(M4)	187	121	64.7	57.4	71.5	0.201	0.167	0.242
		PII(M10)	209	144	68.9	62.1	75.1	0.189	0.163	0.219
	HRV_5.2	PII(M4)	180	104	57.8	50.2	65.1	0.176	0.144	0.215
		PII(M10)	203	140	69.0	62.1	75.3	0.191	0.164	0.222
	HRV_5.8	PII(M4)	180	124	68.9	61.6	75.6	0.207	0.172	0.248
		PII(M10)	206	149	72.3	65.7	78.3	0.183	0.159	0.211
	Pooled HRV groups	PII(M4)	547	349	63.8	59.6	67.8	0.194	0.174	0.217
		PII(M10)	618	433	70.1	66.3	73.7	0.188	0.172	0.204
	Placebo	PII(M4)	186	129	69.4	62.2	75.9	0.253	0.207	0.310
		PII(M10)	207	149	72.0	65.3	78.0	0.194	0.168	0.225
Anti-Tetanus	**HRV_4.7**	PII(M4)	188	184	97.9	94.6	99.4	1.027	0.877	1.201
		PII(M10)	211	211	100.0	98.3	100.0	1.219	1.110	1.338
	HRV_5.2	PII(M4)	180	179	99.4	96.9	100.0	1.107	0.945	1.297
		PII(M10)	204	202	99.0	96.5	99.9	1.119	1.008	1.242
	HRV_5.8	PII(M4)	181	178	98.3	95.2	99.7	1.046	0.893	1.224
		PII(M10)	207	206	99.5	97.3	100.0	1.136	1.022	1.263
	Pooled HRV groups	PII(M4)	549	541	98.5	97.1	99.4	1.059	0.967	1.159
		PII(M10)	622	619	99.5	98.6	99.9	1.158	1.092	1.227
	Placebo	PII(M4)	187	186	99.5	97.1	100.0	1.137	0.969	1.335
		PII(M10)	208	208	100.0	98.2	100.0	1.090	0.987	1.205

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = blood sample taken at the end of the first efficacy period

Supplement 164: Seropositivity rates and anti-BPT antibody GMCs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 15 EL.U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PII(M4)	185	117	63.2	55.9	70.2	18.5	16.5	20.7
	PII(M10)	210	155	73.8	67.3	79.6	22.2	20.0	24.6
HRV_5.2	PII(M4)	177	104	58.8	51.1	66.1	18.4	16.3	20.9
	PII(M10)	205	155	75.6	69.1	81.3	23.0	20.6	25.8
HRV_5.8	PII(M4)	182	111	61.0	53.5	68.1	17.9	16.0	20.1
	PII(M10)	207	143	69.1	62.3	75.3	21.5	19.2	24.2
Pooled HRV groups	PII(M4)	544	332	61.0	56.8	65.1	18.3	17.1	19.6
	PII(M10)	622	453	72.8	69.2	76.3	22.2	20.9	23.7
Placebo	PII(M4)	182	109	59.9	52.4	67.1	17.6	15.6	19.8
	PII(M10)	207	147	71.0	64.3	77.1	21.9	19.5	24.6

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered seropositive level
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = blood sample taken at the end of the first efficacy period

Supplement 165: Seroprotection rates and anti-HBs antibody GMCs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 10 mIU/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PII(M4)	188	185	98.4	95.4	99.7	524.570	435.165	632.345
	PII(M10)	210	201	95.7	92.0	98.0	213.467	176.657	257.948
HRV_5.2	PII(M4)	180	178	98.9	96.0	99.9	568.009	462.879	697.017
	PII(M10)	204	196	96.1	92.4	98.3	200.809	166.402	242.330
HRV_5.8	PII(M4)	184	179	97.3	93.8	99.1	515.978	421.350	631.857
	PII(M10)	207	201	97.1	93.8	98.9	213.276	177.723	255.941
Pooled HRV groups	PII(M4)	552	542	98.2	96.7	99.1	535.402	477.887	599.838
	PII(M10)	621	598	96.3	94.5	97.6	209.161	187.908	232.817
Placebo	PII(M4)	186	183	98.4	95.4	99.7	630.142	515.361	770.488
	PII(M10)	208	203	97.6	94.5	99.2	235.141	197.582	279.839

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = blood sample taken at the end of the first efficacy period

Supplement 166: Seroprotection rates and anti-PRP antibody GMCs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 0.15 mcg/ml				≥ 1 mcg/ml				GMC		
					95% CI		n	%	95% CI		Value	95% CI	
			n	%	LL	UL			LL	UL		LL	UL
HRV_4.7	PII(M4)	184	184	100.0	98.0	100.0	175	95.1	90.9	97.7	6.128	5.193	7.231
	PII(M10)	210	209	99.5	97.4	100.0	196	93.3	89.1	96.3	3.878	3.450	4.358
HRV_5.2	PII(M4)	180	179	99.4	96.9	100.0	159	88.3	82.7	92.6	5.399	4.468	6.523
	PII(M10)	203	202	99.5	97.3	100.0	189	93.1	88.7	96.2	3.957	3.496	4.479
HRV_5.8	PII(M4)	183	181	98.9	96.1	99.9	167	91.3	86.2	94.9	4.634	3.899	5.507
	PII(M10)	207	207	100.0	98.2	100.0	192	92.8	88.3	95.9	3.718	3.301	4.188
Pooled HRV groups	PII(M4)	547	544	99.5	98.4	99.9	501	91.6	88.9	93.8	5.353	4.837	5.924
	PII(M10)	620	618	99.7	98.8	100.0	577	93.1	90.8	94.9	3.849	3.593	4.124
Placebo	PII(M4)	183	182	99.5	97.0	100.0	165	90.2	84.9	94.1	5.379	4.492	6.442
	PII(M10)	205	205	100.0	98.2	100.0	194	94.6	90.6	97.3	3.964	3.496	4.494

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered seroprotective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = blood sample taken at the end of the first efficacy period

Supplement 167: Seroprotection rates and anti-poliovirus types 1, 2 and 3 GMTs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Antibody	Group	Timing	N	≥ 1:8 dilution				GMC		
						95% CI		Value	95% CI	
				n	%	LL	UL		LL	UL
Anti-Polio 1	HRV_4.7	PII(M4)	187	185	98.9	96.2	99.9	1536.6	1230.4	1919.0
		PII(M10)	199	197	99.0	96.4	99.9	788.7	665.6	934.6
	HRV_5.2	PII(M4)	178	173	97.2	93.6	99.1	1041.9	816.9	1329.0
		PII(M10)	190	189	99.5	97.1	100.0	703.3	590.0	838.3
	HRV_5.8	PII(M4)	183	180	98.4	95.3	99.7	1205.1	973.1	1492.5
		PII(M10)	190	189	99.5	97.1	100.0	663.4	551.0	798.8
	Pooled HRV groups	PII(M4)	548	538	98.2	96.7	99.1	1248.9	1095.9	1423.2
		PII(M10)	579	575	99.3	98.2	99.8	717.7	648.2	794.5
	Placebo	PII(M4)	183	181	98.9	96.1	99.9	1304.8	1059.8	1606.5
		PII(M10)	194	194	100.0	98.1	100.0	655.1	548.6	782.3
Anti-Polio 2	HRV_4.7	PII(M4)	187	184	98.4	95.4	99.7	1076.6	885.7	1308.5
		PII(M10)	209	207	99.0	96.6	99.9	465.2	397.2	544.9
	HRV_5.2	PII(M4)	179	175	97.8	94.4	99.4	964.4	783.2	1187.6
		PII(M10)	201	200	99.5	97.3	100.0	460.0	397.8	532.1
	HRV_5.8	PII(M4)	183	182	99.5	97.0	100.0	1211.8	1015.4	1446.2
		PII(M10)	204	203	99.5	97.3	100.0	497.5	433.2	571.4
	Pooled HRV groups	PII(M4)	549	541	98.5	97.1	99.4	1080.4	966.6	1207.7
		PII(M10)	614	610	99.3	98.3	99.8	474.0	435.4	516.0
	Placebo	PII(M4)	183	181	98.9	96.1	99.9	1029.7	854.6	1240.8
		PII(M10)	206	205	99.5	97.3	100.0	423.4	365.5	490.4
Anti-Polio 3	HRV_4.7	PII(M4)	187	159	85.0	79.1	89.8	165.3	126.8	215.6
		PII(M10)	209	192	91.9	87.3	95.2	121.9	100.7	147.4
	HRV_5.2	PII(M4)	179	151	84.4	78.2	89.3	145.2	109.2	193.1
		PII(M10)	201	183	91.0	86.2	94.6	102.2	83.0	125.8
	HRV_5.8	PII(M4)	183	158	86.3	80.5	91.0	159.8	123.1	207.5
		PII(M10)	204	192	94.1	90.0	96.9	113.6	94.1	137.2
	Pooled HRV groups	PII(M4)	549	468	85.2	82.0	88.1	156.7	134.1	183.0
		PII(M10)	614	567	92.3	90.0	94.3	112.4	100.4	125.8
	Placebo	PII(M4)	183	154	84.2	78.0	89.1	149.7	112.6	199.2
		PII(M10)	206	191	92.7	88.3	95.9	105.2	86.9	127.3

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered seroprotective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = blood sample taken at the end of the first efficacy period

Supplement 168: Summary of demographic characteristics (age calculated in weeks) (total vaccinated cohort receiving three doses of study vaccine)

Characteristics	Parameters or Categories	HRV_4.7 N= 31		HRV_5.2 N= 30		HRV_5.8 N= 30	
		Value or n	%	Value or n	%	Value or n	%
Age at first Dose(weeks)	Mean	9.6	-	10.0	-	9.6	-
	SD	1.78	-	1.53	-	1.38	-
	Median	10	-	10	-	10	-
	Minimum	6	-	7	-	7	-
	Maximum	12	-	12	-	12	-
Gender	Female	21	67.7	10	33.3	10	33.3
	Male	10	32.3	20	66.7	20	66.7
Race	Black	1	3.2	1	3.3	1	3.3
	White/Caucasian	7	22.6	6	20.0	5	16.7
	Other	23	74.2	23	76.7	24	80.0
Height(cm)	Mean	56.8	-	57.1	-	57.7	-
	SD	2.29	-	3.17	-	2.47	-
	Median	57	-	57.5	-	58	-
Weight(kg)	Mean	5.4	-	5.8	-	5.7	-
	SD	0.63	-	0.97	-	0.79	-
	Median	5.4	-	5.6	-	5.55	-

Characteristics	Parameters or Categories	Placebo N= 30		Total N= 121	
		Value or n	%	Value or n	%
Age at first Dose(weeks)	Mean	10.1	-	9.8	-
	SD	1.53	-	1.60	-
	Median	11	-	10	-
	Minimum	6	-	6	-
	Maximum	12	-	12	-
Gender	Female	12	40.0	53	43.8
	Male	18	60.0	68	56.2
Race	Black	0	0.0	3	2.5
	White/Caucasian	6	20.0	24	19.8
	Other	24	80.0	94	77.7
Height(cm)	Mean	57.2	-	57.2	-
	SD	2.85	-	2.70	-
	Median	57	-	57	-
Weight(kg)	Mean	5.8	-	5.6	-
	SD	0.84	-	0.80	-
	Median	5.7	-	5.5	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

Supplement 169: Increase in height and weight from Visit 1 to Visit 2, 3, 4 and 5 (total vaccinated cohort receiving three doses of study vaccine)

Visit	Characteristics	Parameters or Categories	HRV _4.7 N = (31)	HRV_5.2 N = (30)	HRV_5.8 N = (30)	Placebo N = (30)	Total N = (121)
			Value	Value	Value	Value	Value
Visit 2	Increase in height (cm) from Visit 1	Mean	6.2	6.0	5.0	5.6	5.7
		SD	2.67	2.86	3.01	1.81	2.63
		Median	6	6	5.5	5.5	6
		Unknown	1	0	0	0	1
	Increase in weight (kg) from Visit 1	Mean	1.5	1.5	1.5	1.4	1.5
		SD	0.4	0.55	0.41	0.49	0.46
		Median	1.5	1.4	1.4	1.4	1.4
		Unknown	0	0	0	0	0
Visit 3	Increase in height (cm) from Visit 1	Mean	10.5	10.5	9.8	10.1	10.2
		SD	2.96	3.36	2.71	1.68	2.73
		Median	10	10	11	10	10
		Unknown	1	0	0	1	2
	Increase in weight (kg) from Visit 1	Mean	2.4	2.4	2.4	2.5	2.4
		SD	0.7	0.64	0.55	0.74	0.66
		Median	2.5	2.4	2.1	2.4	2.4
		Unknown	0	0	1	0	1
Visit 4	Increase in height (cm) from Visit 1	Mean	13.1	13.1	12.8	13.0	13.0
		SD	3.96	3.11	3.93	2.31	3.36
		Median	12	13	13	13	12.5
		Unknown	0	0	1	0	1
	Increase in weight (kg) from Visit 1	Mean	3.0	2.9	2.9	3.1	3.0
		SD	0.61	0.74	0.73	0.7	0.69
		Median	2.9	2.9	2.8	3	2.9
		Unknown	0	0	1	0	1
Visit 5	Increase in height (cm) from Visit 1	Mean	17.5	16.9	16.5	16.6	16.9
		SD	3.31	3.2	3.76	2.68	3.24
		Median	18	17	17	17.5	17
		Unknown	0	1	0	0	1
	Increase in weight (kg) from Visit 1	Mean	4.0	3.6	3.9	3.9	3.9
		SD	0.65	0.82	0.94	0.93	0.85
		Median	4.1	3.6	3.75	3.85	3.85
		Unknown	0	1	0	0	1

Notes: N = total number of subjects by group or in total (sum of all groups)
value = value of the considered parameter
SD = standard deviation

Supplement 170: Summary of feeding criteria (total vaccinated cohort receiving three doses of study vaccine)

Dose	Group	N	Feeding criteria					
			Breast milk		Infant formula		Both	
			n	%	n	%	n	%
1	HRV_4.7	31	25	80.6	0	0.0	6	19.4
	HRV_5.2	30	21	70.0	0	0.0	9	30.0
	HRV_5.8	30	23	76.7	0	0.0	7	23.3
	Placebo	30	22	73.3	0	0.0	8	26.7
2	HRV_4.7	31	14	45.2	1	3.2	16	51.6
	HRV_5.2	30	17	56.7	1	3.3	12	40.0
	HRV_5.8	30	18	60.0	0	0.0	12	40.0
	Placebo	30	20	66.7	2	6.7	8	26.7
3	HRV_4.7	31	4	12.9	2	6.5	25	80.6
	HRV_5.2	30	5	16.7	3	10.0	22	73.3
	HRV_5.8	30	3	10.0	1	3.3	26	86.7
	Placebo	30	5	16.7	4	13.3	21	70.0

Notes: N = number of subjects having received the considered dose and with available data
n/% = number/percentage of subjects with the specified feeding criteria

Supplement 171: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	31	6	19.4	7.5	37.5
	HRV_5.2	30	6	20.0	7.7	38.6
	HRV_5.8	30	4	13.3	3.8	30.7
	Pooled HRV groups	91	16	17.6	10.4	27.0
	Placebo	30	7	23.3	9.9	42.3
Dose 2	**HRV_4.7**	31	9	29.0	14.2	48.0
	HRV_5.2	30	9	30.0	14.7	49.4
	HRV_5.8	30	5	16.7	5.6	34.7
	Pooled HRV groups	91	23	25.3	16.7	35.5
	Placebo	30	4	13.3	3.8	30.7
Dose 3	**HRV_4.7**	31	7	22.6	9.6	41.1
	HRV_5.2	30	6	20.0	7.7	38.6
	HRV_5.8	30	8	26.7	12.3	45.9
	Pooled HRV groups	91	21	23.1	14.9	33.1
	Placebo	30	7	23.3	9.9	42.3
Overall/dose	**HRV_4.7**	93	22	23.7	15.5	33.6
	HRV_5.2	90	21	23.3	15.1	33.4
	HRV_5.8	90	17	18.9	11.4	28.5
	Pooled HRV groups	273	60	22.0	17.2	27.4
	Placebo	90	18	20.0	12.3	29.8
Overall/subject	**HRV_4.7**	31	14	45.2	27.3	64.0
	HRV_5.2	30	13	43.3	25.5	62.6
	HRV_5.8	30	14	46.7	28.3	65.7
	Pooled HRV groups	91	41	45.1	34.6	55.8
	Placebo	30	14	46.7	28.3	65.7

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 172: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up (total vaccinated cohort for safety receiving three doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	31	29	93.5	78.6	99.2
	HRV_5.2	30	29	96.7	82.8	99.9
	HRV_5.8	30	28	93.3	77.9	99.2
	Pooled HRV groups	91	86	94.5	87.6	98.2
	Placebo	30	27	90.0	73.5	97.9
Dose 2	**HRV_4.7**	31	25	80.6	62.5	92.5
	HRV_5.2	30	21	70.0	50.6	85.3
	HRV_5.8	30	25	83.3	65.3	94.4
	Pooled HRV groups	91	71	78.0	68.1	86.0
	Placebo	30	28	93.3	77.9	99.2
Dose 3	**HRV_4.7**	31	28	90.3	74.2	98.0
	HRV_5.2	30	22	73.3	54.1	87.7
	HRV_5.8	30	24	80.0	61.4	92.3
	Pooled HRV groups	91	74	81.3	71.8	88.7
	Placebo	30	25	83.3	65.3	94.4
Overall/dose	**HRV_4.7**	93	82	88.2	79.8	93.9
	HRV_5.2	90	72	80.0	70.2	87.7
	HRV_5.8	90	77	85.6	76.6	92.1
	Pooled HRV groups	273	231	84.6	79.8	88.7
	Placebo	90	80	88.9	80.5	94.5
Overall/subject	**HRV_4.7**	31	31	100.0	88.8	100.0
	HRV_5.2	30	30	100.0	88.4	100.0
	HRV_5.8	30	29	96.7	82.8	99.9
	Pooled HRV groups	91	90	98.9	94.0	100.0
	Placebo	30	30	100.0	88.4	100.0

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 173: Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" and grade "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine)

Dose Group		Overall/dose											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		93				90				90			
COUGH	Total	64	68.8	58.4	78.0	72	80.0	70.2	87.7	72	80.0	70.2	87.7
	Grade 2*3	31	33.3	23.9	43.9	36	40.0	29.8	50.9	37	41.1	30.8	52.0
	Grade 3	8	8.6	3.8	16.2	12	13.3	7.1	22.1	6	6.7	2.5	13.9
	Related	30	32.3	22.9	42.7	33	36.7	26.8	47.5	33	36.7	26.8	47.5
DIARRHEA	Total	16	17.2	10.2	26.4	11	12.2	6.3	20.8	19	21.1	13.2	31.0
	Grade 2*3	11	11.8	6.1	20.2	4	4.4	1.2	11.0	14	15.6	8.8	24.7
	Grade 3	7	7.5	3.1	14.9	1	1.1	0.0	6.0	3	3.3	0.7	9.4
	Related	12	12.9	6.8	21.5	8	8.9	3.9	16.8	14	15.6	8.8	24.7
IRRITABILITY	Total	63	67.7	57.3	77.1	57	63.3	52.5	73.2	61	67.8	57.1	77.2
	Grade 2*3	38	40.9	30.8	51.5	40	44.4	34.0	55.3	38	42.2	31.9	53.1
	Grade 3	9	9.7	4.5	17.6	7	7.8	3.2	15.4	6	6.7	2.5	13.9
	Related	59	63.4	52.8	73.2	51	56.7	45.8	67.1	56	62.2	51.4	72.2
LOSS OF APPETITE	Total	31	33.3	23.9	43.9	30	33.3	23.7	44.1	28	31.1	21.8	41.7
	Grade 2*3	12	12.9	6.8	21.5	12	13.3	7.1	22.1	11	12.2	6.3	20.8
	Grade 3	2	2.2	0.3	7.6	2	2.2	0.3	7.8	2	2.2	0.3	7.8
	Related	20	21.5	13.7	31.2	22	24.4	16.0	34.6	26	28.9	19.8	39.4
FEVER	Total	61	65.6	55.0	75.1	49	54.4	43.6	65.0	52	57.8	46.9	68.1
	Grade 2*3	28	30.1	21.0	40.5	22	24.4	16.0	34.6	25	27.8	18.9	38.2
	Grade 3	3	3.2	0.7	9.1	2	2.2	0.3	7.8	3	3.3	0.7	9.4
	Related	58	62.4	51.7	72.2	43	47.8	37.1	58.6	48	53.3	42.5	63.9
VOMITING	Total	28	30.1	21.0	40.5	28	31.1	21.8	41.7	25	27.8	18.9	38.2
	Grade 2*3	14	15.1	8.5	24.0	14	15.6	8.8	24.7	10	11.1	5.5	19.5
	Grade 3	5	5.4	1.8	12.1	4	4.4	1.2	11.0	3	3.3	0.7	9.4
	Related	20	21.5	13.7	31.2	23	25.6	16.9	35.8	17	18.9	11.4	28.5

Notes: For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 173 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" and grade "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine)

Dose		Overall/dose							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		273				90			
COUGH	Total	208	76.2	70.7	81.1	64	71.1	60.6	80.2
	Grade 2*3	104	38.1	32.3	44.1	34	37.8	27.8	48.6
	Grade 3	26	9.5	6.3	13.6	6	6.7	2.5	13.9
	Related	96	35.2	29.5	41.1	35	38.9	28.8	49.7
DIARRHEA	Total	46	16.8	12.6	21.8	16	17.8	10.5	27.3
	Grade 2*3	29	10.6	7.2	14.9	9	10.0	4.7	18.1
	Grade 3	11	4.0	2.0	7.1	2	2.2	0.3	7.8
	Related	34	12.5	8.8	17.0	12	13.3	7.1	22.1
IRRITABILITY	Total	181	66.3	60.4	71.9	62	68.9	58.3	78.2
	Grade 2*3	116	42.5	36.6	48.6	39	43.3	32.9	54.2
	Grade 3	22	8.1	5.1	11.9	7	7.8	3.2	15.4
	Related	166	60.8	54.7	66.6	55	61.1	50.3	71.2
LOSS OF APPETITE	Total	89	32.6	27.1	38.5	30	33.3	23.7	44.1
	Grade 2*3	35	12.8	9.1	17.4	16	17.8	10.5	27.3
	Grade 3	6	2.2	0.8	4.7	1	1.1	0.0	6.0
	Related	68	24.9	19.9	30.5	23	25.6	16.9	35.8
FEVER	Total	162	59.3	53.3	65.2	46	51.1	40.3	61.8
	Grade 2*3	75	27.5	22.3	33.2	14	15.6	8.8	24.7
	Grade 3	8	2.9	1.3	5.7	1	1.1	0.0	6.0
	Related	149	54.6	48.5	60.6	40	44.4	34.0	55.3
VOMITING	Total	81	29.7	24.3	35.5	19	21.1	13.2	31.0
	Grade 2*3	38	13.9	10.0	18.6	12	13.3	7.1	22.1
	Grade 3	12	4.4	2.3	7.6	3	3.3	0.7	9.4
	Related	60	22.0	17.2	27.4	14	15.6	8.8	24.7

Notes: For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 173 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" and grade "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine)

Dose Group		Overall/subject											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		31				30				30			
COUGH	Total	28	90.3	74.2	98.0	28	93.3	77.9	99.2	29	96.7	82.8	99.9
	Grade 2*3	18	58.1	39.1	75.5	23	76.7	57.7	90.1	20	66.7	47.2	82.7
	Grade 3	5	16.1	5.5	33.7	9	30.0	14.7	49.4	4	13.3	3.8	30.7
	Related	21	67.7	48.6	83.3	19	63.3	43.9	80.1	21	70.0	50.6	85.3
DIARRHEA	Total	13	41.9	24.5	60.9	9	30.0	14.7	49.4	12	40.0	22.7	59.4
	Grade 2*3	9	29.0	14.2	48.0	4	13.3	3.8	30.7	11	36.7	19.9	56.1
	Grade 3	6	19.4	7.5	37.5	1	3.3	0.1	17.2	3	10.0	2.1	26.5
	Related	11	35.5	19.2	54.6	7	23.3	9.9	42.3	9	30.0	14.7	49.4
IRRITABILITY	Total	29	93.5	78.6	99.2	28	93.3	77.9	99.2	29	96.7	82.8	99.9
	Grade 2*3	21	67.7	48.6	83.3	24	80.0	61.4	92.3	22	73.3	54.1	87.7
	Grade 3	6	19.4	7.5	37.5	6	20.0	7.7	38.6	5	16.7	5.6	34.7
	Related	27	87.1	70.2	96.4	27	90.0	73.5	97.9	29	96.7	82.8	99.9
LOSS OF APPETITE	Total	17	54.8	36.0	72.7	19	63.3	43.9	80.1	19	63.3	43.9	80.1
	Grade 2*3	9	29.0	14.2	48.0	8	26.7	12.3	45.9	9	30.0	14.7	49.4
	Grade 3	2	6.5	0.8	21.4	2	6.7	0.8	22.1	2	6.7	0.8	22.1
	Related	15	48.4	30.2	66.9	16	53.3	34.3	71.7	19	63.3	43.9	80.1
FEVER	Total	30	96.8	83.3	99.9	27	90.0	73.5	97.9	26	86.7	69.3	96.2
	Grade 2*3	17	54.8	36.0	72.7	13	43.3	25.5	62.6	16	53.3	34.3	71.7
	Grade 3	2	6.5	0.8	21.4	2	6.7	0.8	22.1	3	10.0	2.1	26.5
	Related	30	96.8	83.3	99.9	25	83.3	65.3	94.4	26	86.7	69.3	96.2
VOMITING	Total	17	54.8	36.0	72.7	19	63.3	43.9	80.1	15	50.0	31.3	68.7
	Grade 2*3	10	32.3	16.7	51.4	10	33.3	17.3	52.8	8	26.7	12.3	45.9
	Grade 3	4	12.9	3.6	29.8	4	13.3	3.8	30.7	3	10.0	2.1	26.5
	Related	14	45.2	27.3	64.0	18	60.0	40.6	77.3	11	36.7	19.9	56.1

Notes: For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 173 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" and grade "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine)

Dose		Overall/subject							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		91				30			
COUGH	Total	85	93.4	86.2	97.5	28	93.3	77.9	99.2
	Grade 2*3	61	67.0	56.4	76.5	19	63.3	43.9	80.1
	Grade 3	18	19.8	12.2	29.4	5	16.7	5.6	34.7
	Related	61	67.0	56.4	76.5	22	73.3	54.1	87.7
DIARRHEA	Total	34	37.4	27.4	48.1	12	40.0	22.7	59.4
	Grade 2*3	24	26.4	17.7	36.7	8	26.7	12.3	45.9
	Grade 3	10	11.0	5.4	19.3	2	6.7	0.8	22.1
	Related	27	29.7	20.5	40.2	9	30.0	14.7	49.4
IRRITABILITY	Total	86	94.5	87.6	98.2	28	93.3	77.9	99.2
	Grade 2*3	67	73.6	63.3	82.3	23	76.7	57.7	90.1
	Grade 3	17	18.7	11.3	28.2	6	20.0	7.7	38.6
	Related	83	91.2	83.4	96.1	27	90.0	73.5	97.9
LOSS OF APPETITE	Total	55	60.4	49.6	70.5	19	63.3	43.9	80.1
	Grade 2*3	26	28.6	19.6	39.0	12	40.0	22.7	59.4
	Grade 3	6	6.6	2.5	13.8	1	3.3	0.1	17.2
	Related	50	54.9	44.2	65.4	18	60.0	40.6	77.3
FEVER	Total	83	91.2	83.4	96.1	28	93.3	77.9	99.2
	Grade 2*3	46	50.5	39.9	61.2	14	46.7	28.3	65.7
	Grade 3	7	7.7	3.1	15.2	1	3.3	0.1	17.2
	Related	81	89.0	80.7	94.6	27	90.0	73.5	97.9
VOMITING	Total	51	56.0	45.2	66.4	12	40.0	22.7	59.4
	Grade 2*3	28	30.8	21.5	41.3	8	26.7	12.3	45.9
	Grade 3	11	12.1	6.2	20.6	3	10.0	2.1	26.5
	Related	43	47.3	36.7	58.0	10	33.3	17.3	52.8

Notes: For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 174: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 31				HRV_5.2 N = 30				HRV_5.8 N = 30				Pooled HRV groups N = 91				Placebo N = 30			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		28	90.3	74.2	98	29	96.7	82.8	99.9	30	100	88.4	100	87	95.6	89.1	98.8	30	100	88.4	100
Application site (1820)	Injection site reaction (0058)	2	6.5	0.8	21.4	1	3.3	0.1	17.2	1	3.3	0.1	17.2	4	4.4	1.2	10.9	3	10	2.1	26.5
	Otitis externa (0059)	1	3.2	0.1	16.7	0	0	0	11.6	0	0	0	11.6	1	1.1	0	6	0	0	0	11.6
Body as a whole general (1810)	Allergy (1058)	4	12.9	3.6	29.8	2	6.7	0.8	22.1	2	6.7	0.8	22.1	8	8.8	3.9	16.6	3	10	2.1	26.5
	Fever (0725)	9	29	14.2	48	11	36.7	19.9	56.1	9	30	14.7	49.4	29	31.9	22.5	42.5	14	46.7	28.3	65.7
	Injury (9001)	0	0	0	11.2	0	0	0	11.6	0	0	0	11.6	0	0	0	4	1	3.3	0.1	17.2
Central and peripheral nervous system (410)	Headache (0109)	0	0	0	11.2	1	3.3	0.1	17.2	0	0	0	11.6	1	1.1	0	6	0	0	0	11.6
Gastrointestinal system (600)	Abdominal pain (0268)	0	0	0	11.2	0	0	0	11.6	1	3.3	0.1	17.2	1	1.1	0	6	1	3.3	0.1	17.2
	Anorexia (0165)	1	3.2	0.1	16.7	1	3.3	0.1	17.2	2	6.7	0.8	22.1	4	4.4	1.2	10.9	2	6.7	0.8	22.1
	Constipation (0204)	0	0	0	11.2	1	3.3	0.1	17.2	2	6.7	0.8	22.1	3	3.3	0.7	9.3	1	3.3	0.1	17.2
	Gastroenteritis (0293)	1	3.2	0.1	16.7	0	0	0	11.6	2	6.7	0.8	22.1	3	3.3	0.7	9.3	3	10	2.1	26.5
	Gastrointestinal disorder nos (1262)	0	0	0	11.2	1	3.3	0.1	17.2	1	3.3	0.1	17.2	2	2.2	0.3	7.7	0	0	0	11.6
	Stomatitis (0327)	0	0	0	11.2	0	0	0	11.6	1	3.3	0.1	17.2	1	1.1	0	6	1	3.3	0.1	17.2
	Vomiting (0228)	4	12.9	3.6	29.8	4	13.3	3.8	30.7	6	20	7.7	38.6	14	15.4	8.7	24.5	3	10	2.1	26.5
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	11.2	0	0	0	11.6	0	0	0	11.6	0	0	0	4	1	3.3	0.1	17.2
	Earache (0260)	1	3.2	0.1	16.7	0	0	0	11.6	0	0	0	11.6	1	1.1	0	6	1	3.3	0.1	17.2
Psychiatric (500)	Nervousness (0188)	0	0	0	11.2	1	3.3	0.1	17.2	0	0	0	11.6	1	1.1	0	6	0	0	0	11.6

Notes: N = number of subjects having received at least one dose
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 174 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 31				HRV_5.2 N = 30				HRV_5.8 N = 30				Pooled HRV groups N = 91				Placebo N = 30			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Red blood cell (1210)	Anemia (0544)	0	0	0	11.2	1	3.3	0.1	17.2	0	0	0	11.6	1	1.1	0	6	1	3.3	0.1	17.2
Resistance mechanism (1830)	Abscess (0887)	0	0	0	11.2	0	0	0	11.6	1	3.3	0.1	17.2	1	1.1	0	6	0	0	0	11.6
	Infection (0736)	4	12.9	3.6	29.8	3	10	2.1	26.5	5	16.7	5.6	34.7	12	13.2	7	21.9	7	23.3	9.9	42.3
	Infection viral (0740)	26	83.9	66.3	94.5	19	63.3	43.9	80.1	22	73.3	54.1	87.7	67	73.6	63.3	82.3	27	90	73.5	97.9
	Moniliasis (0741)	1	3.2	0.1	16.7	0	0	0	11.6	2	6.7	0.8	22.1	3	3.3	0.7	9.3	1	3.3	0.1	17.2
	Otitis media (0750)	0	0	0	11.2	2	6.7	0.8	22.1	2	6.7	0.8	22.1	4	4.4	1.2	10.9	1	3.3	0.1	17.2
	Upper resp tract infection(0543)	6	19.4	7.5	37.5	11	36.7	19.9	56.1	5	16.7	5.6	34.7	22	24.2	15.8	34.3	2	6.7	0.8	22.1
Respiratory system (1100)	Asthma (1367)	1	3.2	0.1	16.7	0	0	0	11.6	0	0	0	11.6	1	1.1	0	6	1	3.3	0.1	17.2
	Bronchitis (0805)	6	19.4	7.5	37.5	5	16.7	5.6	34.7	6	20	7.7	38.6	17	18.7	11.3	28.2	5	16.7	5.6	34.7
	Coughing (0513)	9	29	14.2	48	9	30	14.7	49.4	6	20	7.7	38.6	24	26.4	17.7	36.7	9	30	14.7	49.4
	Pharyngitis (0523)	2	6.5	0.8	21.4	1	3.3	0.1	17.2	1	3.3	0.1	17.2	4	4.4	1.2	10.9	4	13.3	3.8	30.7
	Pneumonia (0528)	1	3.2	0.1	16.7	5	16.7	5.6	34.7	0	0	0	11.6	6	6.6	2.5	13.8	1	3.3	0.1	17.2
	Rhinitis (0539)	3	9.7	2	25.8	2	6.7	0.8	22.1	4	13.3	3.8	30.7	9	9.9	4.6	17.9	3	10	2.1	26.5
	Sputum increased (0541)	0	0	0	11.2	0	0	0	11.6	0	0	0	11.6	0	0	0	4	1	3.3	0.1	17.2
	Stridor (0542)	0	0	0	11.2	0	0	0	11.6	1	3.3	0.1	17.2	1	1.1	0	6	0	0	0	11.6

Notes: N = number of subjects having received at least one dose
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 174 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 31				HRV_5.2 N = 30				HRV_5.8 N = 30				Pooled HRV groups N = 91				Placebo N = 30			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Skin and appendages (100)	Dermatitis (0007)	0	0	0	11.2	2	6.7	0.8	22.1	1	3.3	0.1	17.2	3	3.3	0.7	9.3	0	0	0	11.6
	Furunculosis (0016)	1	3.2	0.1	16.7	2	6.7	0.8	22.1	2	6.7	0.8	22.1	5	5.5	1.8	12.4	3	10	2.1	26.5
	Pruritus (0024)	0	0	0	11.2	2	6.7	0.8	22.1	0	0	0	11.6	2	2.2	0.3	7.7	1	3.3	0.1	17.2
	Rash erythematous (0028)	0	0	0	11.2	0	0	0	11.6	1	3.3	0.1	17.2	1	1.1	0	6	0	0	0	11.6
	Rash pustular (0032)	0	0	0	11.2	2	6.7	0.8	22.1	2	6.7	0.8	22.1	4	4.4	1.2	10.9	0	0	0	11.6
	Skin disorder (0037)	3	9.7	2	25.8	1	3.3	0.1	17.2	3	10	2.1	26.5	7	7.7	3.1	15.2	4	13.3	3.8	30.7
	Sweat gland disorder(1166)	0	0	0	11.2	2	6.7	0.8	22.1	2	6.7	0.8	22.1	4	4.4	1.2	10.9	0	0	0	11.6
Urinary system (1300)	Dysuria (0601)	0	0	0	11.2	0	0	0	11.6	1	3.3	0.1	17.2	1	1.1	0	6	0	0	0	11.6
	Urinary retention (0157)	0	0	0	11.2	0	0	0	11.6	0	0	0	11.6	0	0	0	4	1	3.3	0.1	17.2
	Urinary tract infection (0628)	0	0	0	11.2	0	0	0	11.6	0	0	0	11.6	0	0	0	4	1	3.3	0.1	17.2
Vision (431)	Conjunctivitis (0238)	0	0	0	11.2	3	10	2.1	26.5	1	3.3	0.1	17.2	4	4.4	1.2	10.9	3	10	2.1	26.5

Notes: N = number of subjects having received at least one dose
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 175: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 93				HRV_5.2 D = 90				HRV_5.8 D = 90				Pooled HRV groups D = 273				Placebo D = 90			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		64	68.8	58.4	78	74	82.2	72.7	89.5	64	71.1	60.6	80.2	202	74	68.4	79.1	70	77.8	67.8	85.9
Application site (1820)	Injection site reaction (0058)	2	2.2	0.3	7.6	1	1.1	0	6	1	1.1	0	6	4	1.5	0.4	3.7	4	4.4	1.2	11
	Otitis externa (0059)	1	1.1	0	5.8	0	0	0	4	0	0	0	4	1	0.4	0	2	0	0	0	4
Body as a whole general (1810)	Allergy (1058)	5	5.4	1.8	12.1	2	2.2	0.3	7.8	3	3.3	0.7	9.4	10	3.7	1.8	6.6	4	4.4	1.2	11
	Fever (0725)	11	11.8	6.1	20.2	13	14.4	7.9	23.4	10	11.1	5.5	19.5	34	12.5	8.8	17	14	15.6	8.8	24.7
	Injury (9001)	0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6
Central and peripheral nervous system (410)	Headache (0109)	0	0	0	3.9	1	1.1	0	6	0	0	0	4	1	0.4	0	2	0	0	0	4
Gastrointestinal system (600)	Abdominal pain (0268)	0	0	0	3.9	0	0	0	4	1	1.1	0	6	1	0.4	0	2	1	1.1	0	6
	Anorexia (0165)	1	1.1	0	5.8	1	1.1	0	6	2	2.2	0.3	7.8	4	1.5	0.4	3.7	3	3.3	0.7	9.4
	Constipation (0204)	0	0	0	3.9	1	1.1	0	6	2	2.2	0.3	7.8	3	1.1	0.2	3.2	1	1.1	0	6
	Gastroenteritis (0293)	1	1.1	0	5.8	0	0	0	4	2	2.2	0.3	7.8	3	1.1	0.2	3.2	3	3.3	0.7	9.4
	Gastrointestinal disorder nos (1262)	0	0	0	3.9	1	1.1	0	6	1	1.1	0	6	2	0.7	0.1	2.6	0	0	0	4
	Stomatitis (0327)	0	0	0	3.9	0	0	0	4	1	1.1	0	6	1	0.4	0	2	1	1.1	0	6
	Vomiting (0228)	4	4.3	1.2	10.6	6	6.7	2.5	13.9	8	8.9	3.9	16.8	18	6.6	4	10.2	3	3.3	0.7	9.4

Supplement 175 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 93				HRV_5.2 D = 90				HRV_5.8 D = 90				Pooled HRV groups D = 273				Placebo D = 90			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6
	Earache (0260)	1	1.1	0	5.8	0	0	0	4	0	0	0	4	1	0.4	0	2	1	1.1	0	6
Psychiatric (500)	Nervousness (0188)	0	0	0	3.9	1	1.1	0	6	0	0	0	4	1	0.4	0	2	0	0	0	4
Red blood cell (1210)	Anemia (0544)	0	0	0	3.9	1	1.1	0	6	0	0	0	4	1	0.4	0	2	1	1.1	0	6
Resistance mechanism (1830)	Abscess (0887)	0	0	0	3.9	0	0	0	4	1	1.1	0	6	1	0.4	0	2	0	0	0	4
	Infection (0736)	4	4.3	1.2	10.6	4	4.4	1.2	11	6	6.7	2.5	13.9	14	5.1	2.8	8.5	9	10	4.7	18.1
	Infection viral (0740)	41	44.1	33.8	54.8	37	41.1	30.8	52	34	37.8	27.8	48.6	112	41	35.1	47.1	39	43.3	32.9	54.2
	Moniliasis (0741)	1	1.1	0	5.8	0	0	0	4	2	2.2	0.3	7.8	3	1.1	0.2	3.2	1	1.1	0	6
	Otitis media (0750)	0	0	0	3.9	3	3.3	0.7	9.4	2	2.2	0.3	7.8	5	1.8	0.6	4.2	1	1.1	0	6
	Upper resp tract infection (0543)	8	8.6	3.8	16.2	12	13.3	7.1	22.1	7	7.8	3.2	15.4	27	9.9	6.6	14.1	2	2.2	0.3	7.8
Respiratory system (1100)	Asthma (1367)	1	1.1	0	5.8	0	0	0	4	0	0	0	4	1	0.4	0	2	1	1.1	0	6
	Bronchitis (0805)	6	6.5	2.4	13.5	5	5.6	1.8	12.5	8	8.9	3.9	16.8	19	7	4.2	10.7	5	5.6	1.8	12.5
	Coughing (0513)	10	10.8	5.3	18.9	10	11.1	5.5	19.5	6	6.7	2.5	13.9	26	9.5	6.3	13.6	13	14.4	7.9	23.4
	Pharyngitis (0523)	2	2.2	0.3	7.6	1	1.1	0	6	1	1.1	0	6	4	1.5	0.4	3.7	5	5.6	1.8	12.5
	Pneumonia (0528)	1	1.1	0	5.8	5	5.6	1.8	12.5	0	0	0	4	6	2.2	0.8	4.7	1	1.1	0	6
	Rhinitis (0539)	3	3.2	0.7	9.1	2	2.2	0.3	7.8	5	5.6	1.8	12.5	10	3.7	1.8	6.6	3	3.3	0.7	9.4
	Sputum increased (0541)	0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6
	Stridor (0542)	0	0	0	3.9	0	0	0	4	1	1.1	0	6	1	0.4	0	2	0	0	0	4

Notes: D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 175 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 93				HRV_5.2 D = 90				HRV_5.8 D = 90				Pooled HRV groups D = 273				Placebo D = 90			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Skin and appendages (100)	Dermatitis (0007)	0	0	0	3.9	2	2.2	0.3	7.8	1	1.1	0	6	3	1.1	0.2	3.2	0	0	0	4
	Furunculosis (0016)	1	1.1	0	5.8	2	2.2	0.3	7.8	3	3.3	0.7	9.4	6	2.2	0.8	4.7	3	3.3	0.7	9.4
	Pruritus (0024)	0	0	0	3.9	3	3.3	0.7	9.4	0	0	0	4	3	1.1	0.2	3.2	1	1.1	0	6
	Rash erythematous (0028)	0	0	0	3.9	0	0	0	4	1	1.1	0	6	1	0.4	0	2	0	0	0	4
	Rash pustular (0032)	0	0	0	3.9	2	2.2	0.3	7.8	2	2.2	0.3	7.8	4	1.5	0.4	3.7	0	0	0	4
	Skin disorder (0037)	3	3.2	0.7	9.1	1	1.1	0	6	3	3.3	0.7	9.4	7	2.6	1	5.2	5	5.6	1.8	12.5
	Sweat gland disorder (1166)	0	0	0	3.9	2	2.2	0.3	7.8	2	2.2	0.3	7.8	4	1.5	0.4	3.7	0	0	0	4
Urinary system (1300)	Dysuria (0601)	0	0	0	3.9	0	0	0	4	1	1.1	0	6	1	0.4	0	2	0	0	0	4
	Urinary retention (0157)	0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6
	Urinary tract infection (0628)	0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6
Vision (431)	Conjunctivitis (0238)	0	0	0	3.9	3	3.3	0.7	9.4	1	1.1	0	6	4	1.5	0.4	3.7	3	3.3	0.7	9.4

Notes: D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 176: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 93				HRV_5.2 D = 90				HRV_5.8 D = 90				Pooled HRV groups D = 273				Placebo D = 90			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6
Respiratory system (1100)	Pneumonia (0528)	0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6

Notes: D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 177: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 93				HRV_5.2 D = 90				HRV_5.8 D = 90				Pooled HRV groups D = 273				Placebo D = 90			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		1	1.1	0	5.8	4	4.4	1.2	11	2	2.2	0.3	7.8	7	2.6	1	5.2	4	4.4	1.2	11
Gastrointestinal system (600)	Gastroenteritis (0293)	1	1.1	0	5.8	0	0	0	4	2	2.2	0.3	7.8	3	1.1	0.2	3.2	3	3.3	0.7	9.4
Respiratory system (1100)	Pneumonia (0528)	0	0	0	3.9	4	4.4	1.2	11	0	0	0	4	4	1.5	0.4	3.7	1	1.1	0	6

Notes: D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 178: Number and percentage of doses and subjects who took at least one concomitant medication from Day 0 to Day 14 after vaccination by type (total vaccinated cohort for safety receiving three doses of study vaccine)

	Overall/dose											
	HRV_4.7 (N=93)				HRV_5.2 (N=90)				HRV_5.8 (N=90)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL				
Any medication	51	54.8	44.2	65.2	43	47.8	37.1	58.6	57	63.3	52.5	73.2
Any antipyretic	48	51.6	41.0	62.1	41	45.6	35.0	56.4	54	60.0	49.1	70.2
Prophylactic antipyretic	0	0.0	0.0	3.9	0	0.0	0.0	4.0	0	0.0	0.0	4.0
Any antibiotic	6	6.5	2.4	13.5	4	4.4	1.2	11.0	3	3.3	0.7	9.4

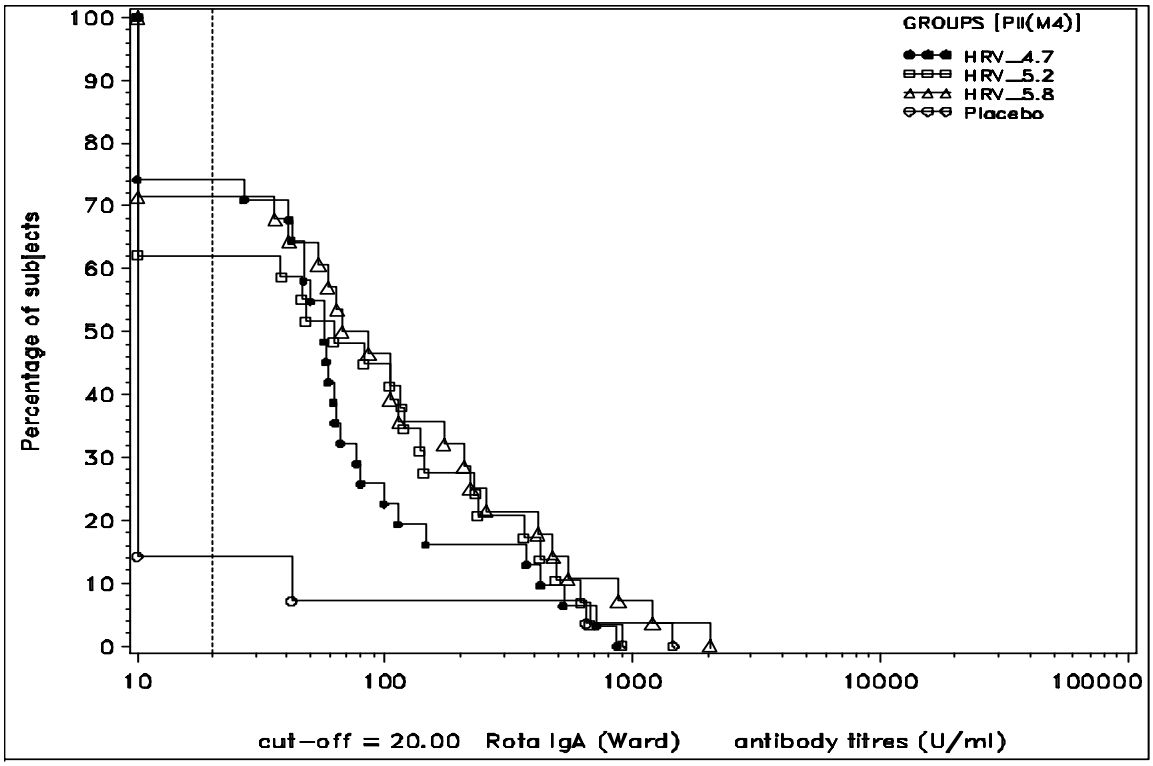
	Pooled HRV groups (N=273)				Placebo (N=90)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL
Any medication	151	55.3	49.2	61.3	46	51.1	40.3	61.8
Any antipyretic	143	52.4	46.3	58.4	45	50.0	39.3	60.7
Prophylactic antipyretic	0	0.0	0.0	1.3	1	1.1	0.0	6.0
Any antibiotic	13	4.8	2.6	8.0	3	3.3	0.7	9.4

	Overall/subject											
	HRV_4.7 (N=31)				HRV_5.2 (N=30)				HRV_5.8 (N=30)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL				
Any medication	25	80.6	62.5	92.5	24	80.0	61.4	92.3	29	96.7	82.8	99.9
Any antipyretic	25	80.6	62.5	92.5	23	76.7	57.7	90.1	29	96.7	82.8	99.9
Prophylactic antipyretic	0	0.0	0.0	11.2	0	0.0	0.0	11.6	0	0.0	0.0	11.6
Any antibiotic	6	19.4	7.5	37.5	3	10.0	2.1	26.5	3	10.0	2.1	26.5

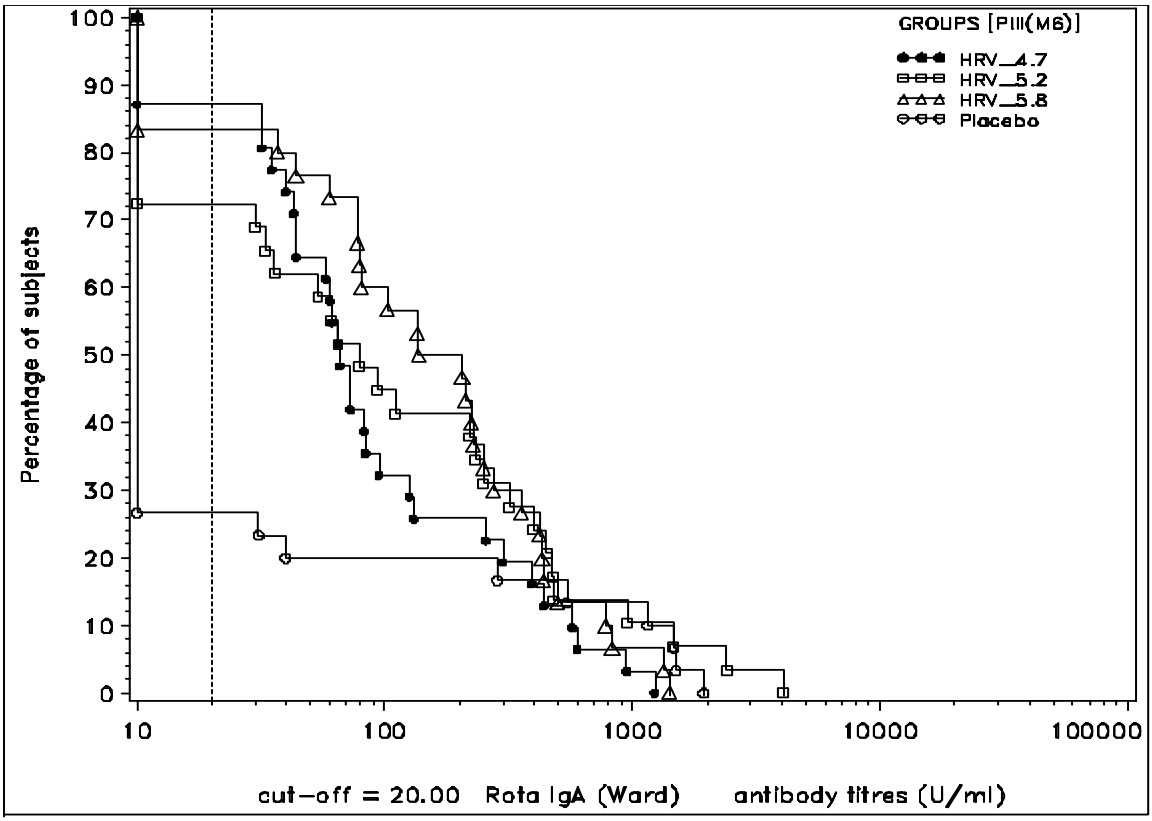
	Pooled HRV groups (N=91)				Placebo (N=30)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL
Any medication	78	85.7	76.8	92.2	24	80.0	61.4	92.3
Any antipyretic	77	84.6	75.5	91.3	24	80.0	61.4	92.3
Prophylactic antipyretic	0	0.0	0.0	4.0	1	3.3	0.1	17.2
Any antibiotic	12	13.2	7.0	21.9	3	10.0	2.1	26.5

Notes: For Overall/dose: N= total number of doses administered
n/% = number/percentage of doses with at least one specified concomitant medication, from Day 0 to Day 14.
For Overall/subject: N= total number of subjects having received at least one dose
n/% = total number/percentage of subject having who started taking the specified concomitant medication at least once after the considered dose, from Day 0 to Day 14
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

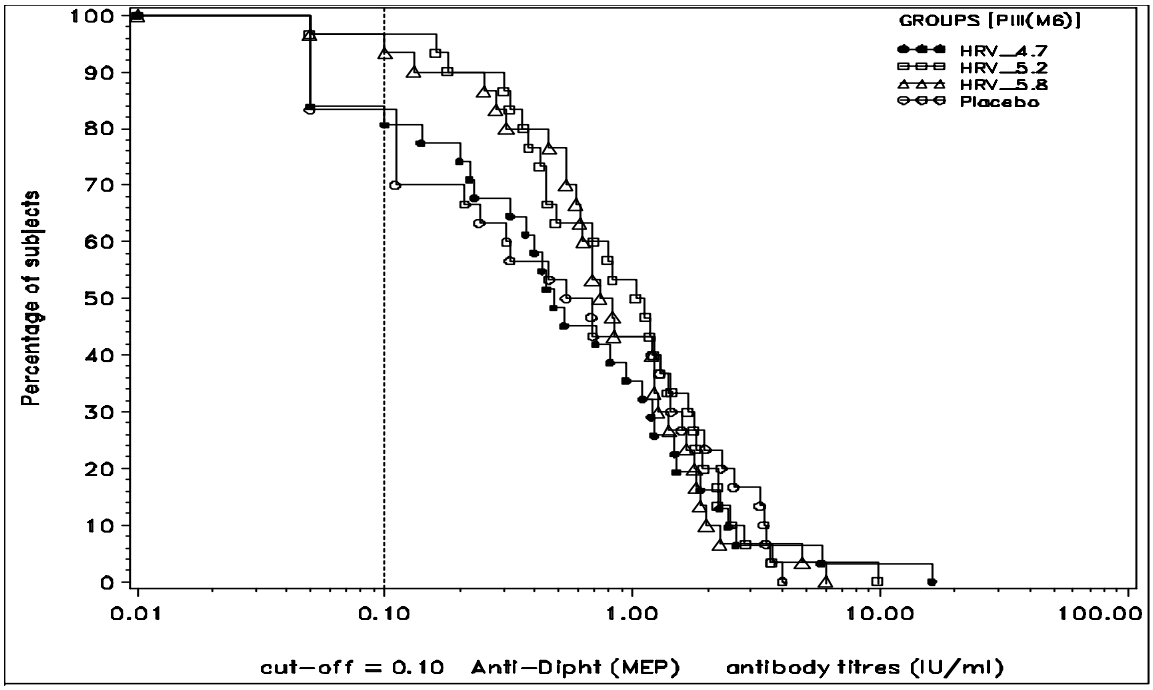
Supplement 179: Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations two months after Dose 2 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



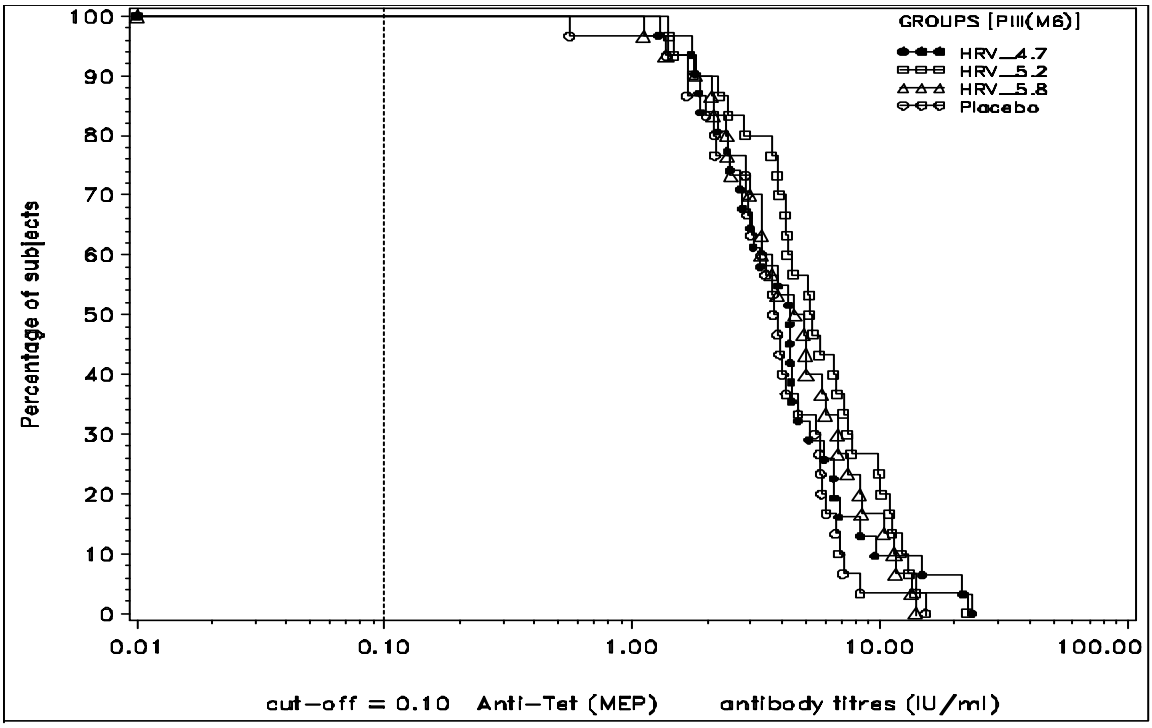
Supplement 180: Reverse cumulative curves for anti-rotavirus IgA antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



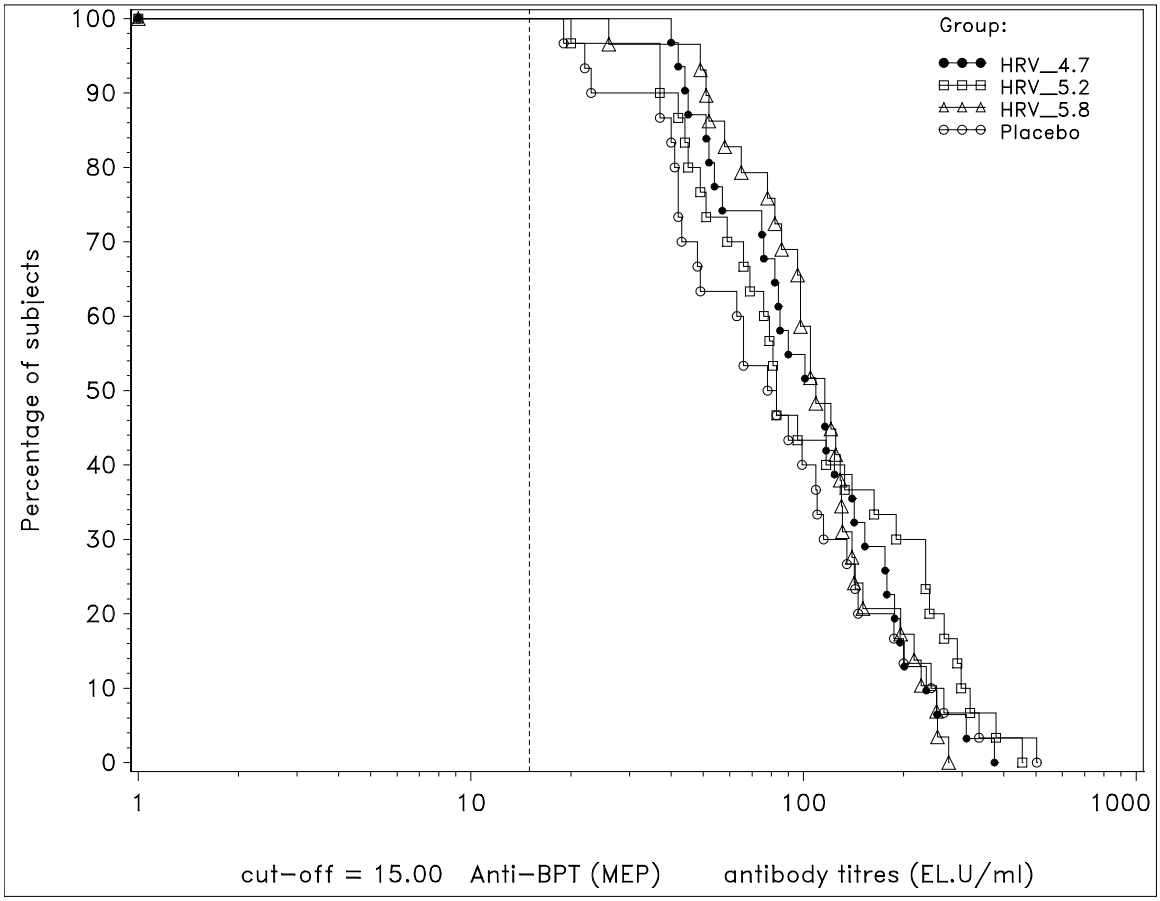
Supplement 181: Reverse cumulative curves for anti-diphtheria antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



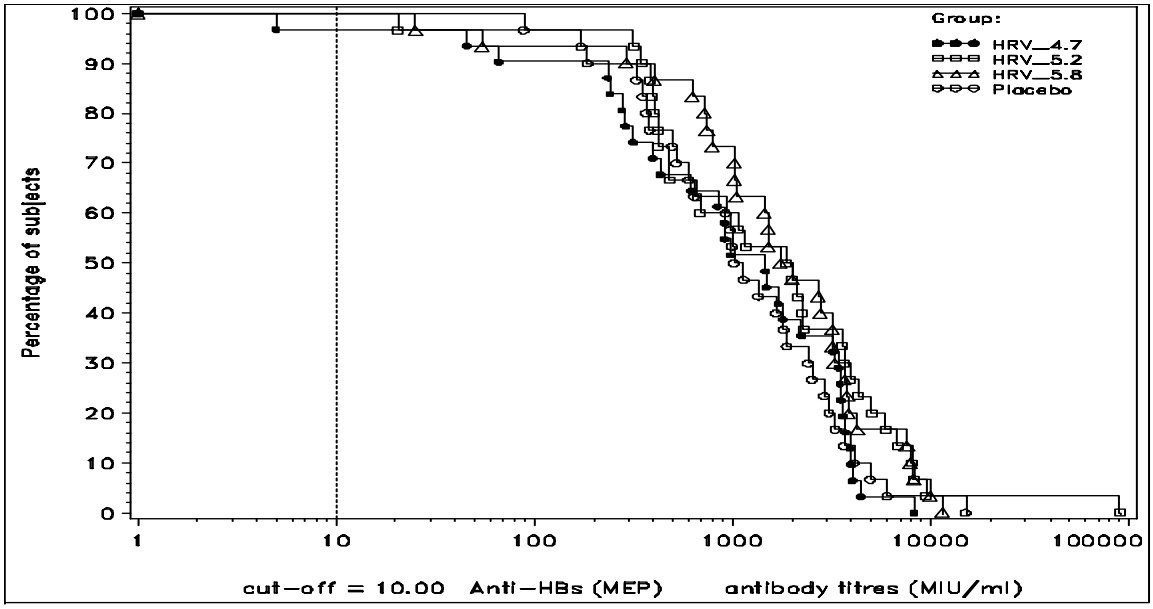
Supplement 182: Reverse cumulative curves for anti-tetanus antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



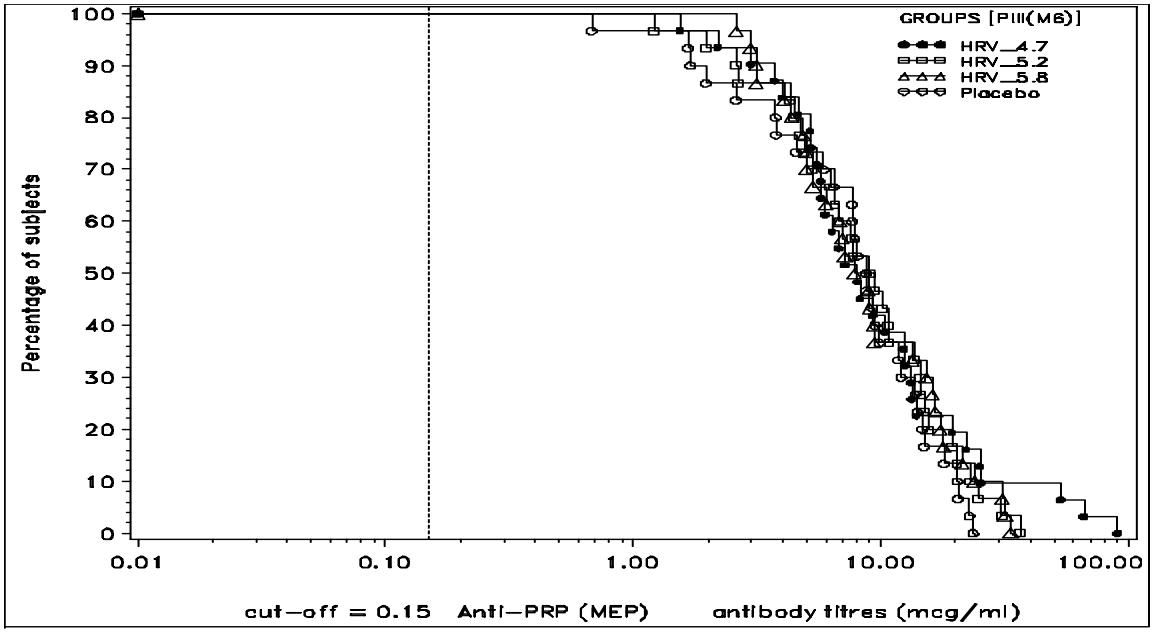
Supplement 183: Reverse cumulative curves for anti-BPT antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



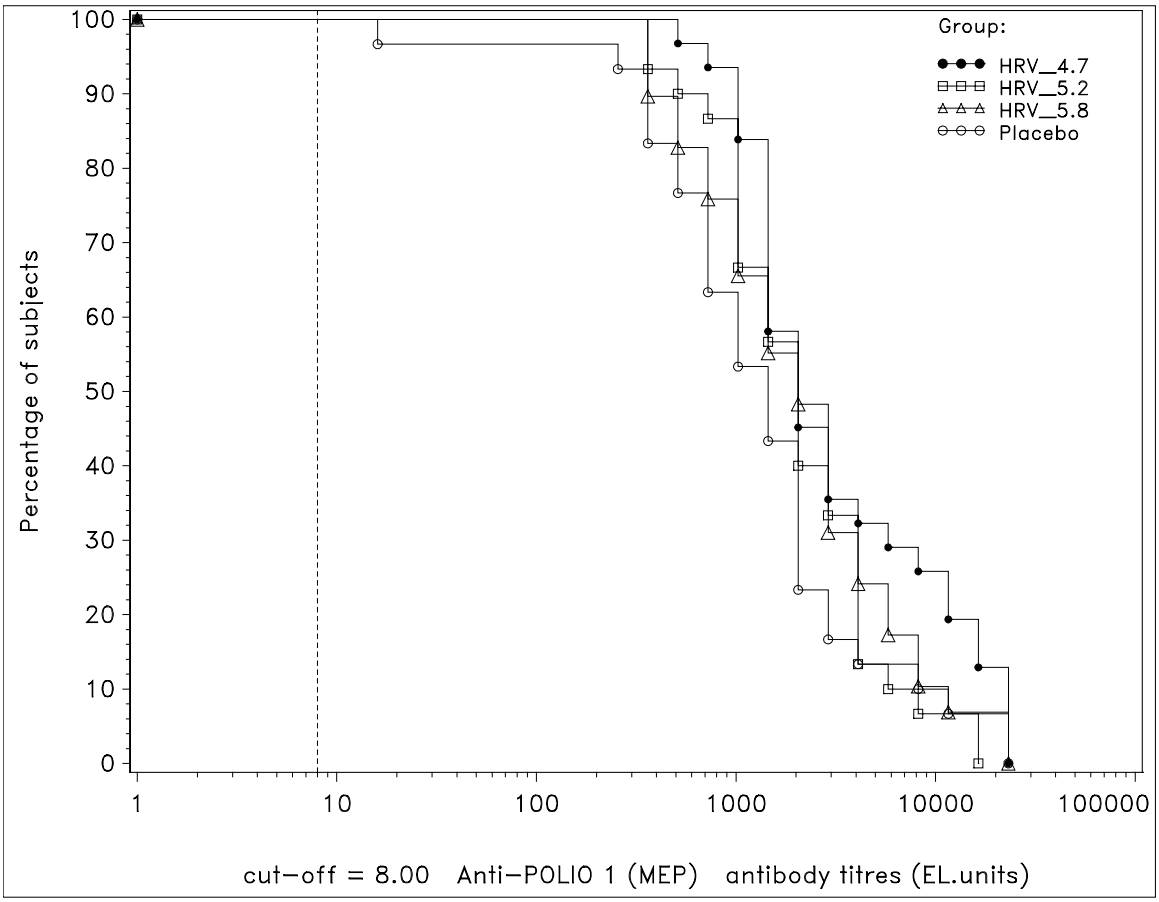
Supplement 184: Reverse cumulative curves for anti-HBs antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



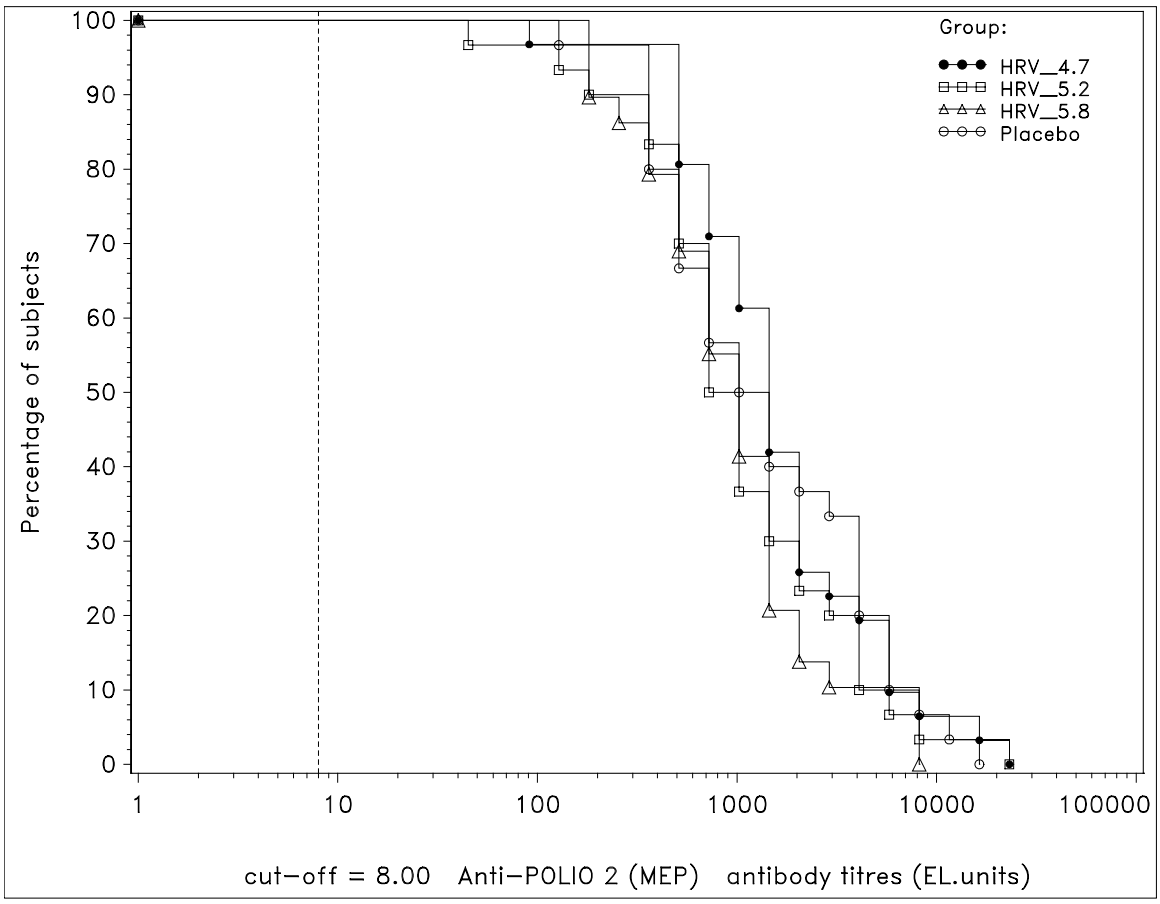
Supplement 185: Reverse cumulative curves for anti-PRP antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



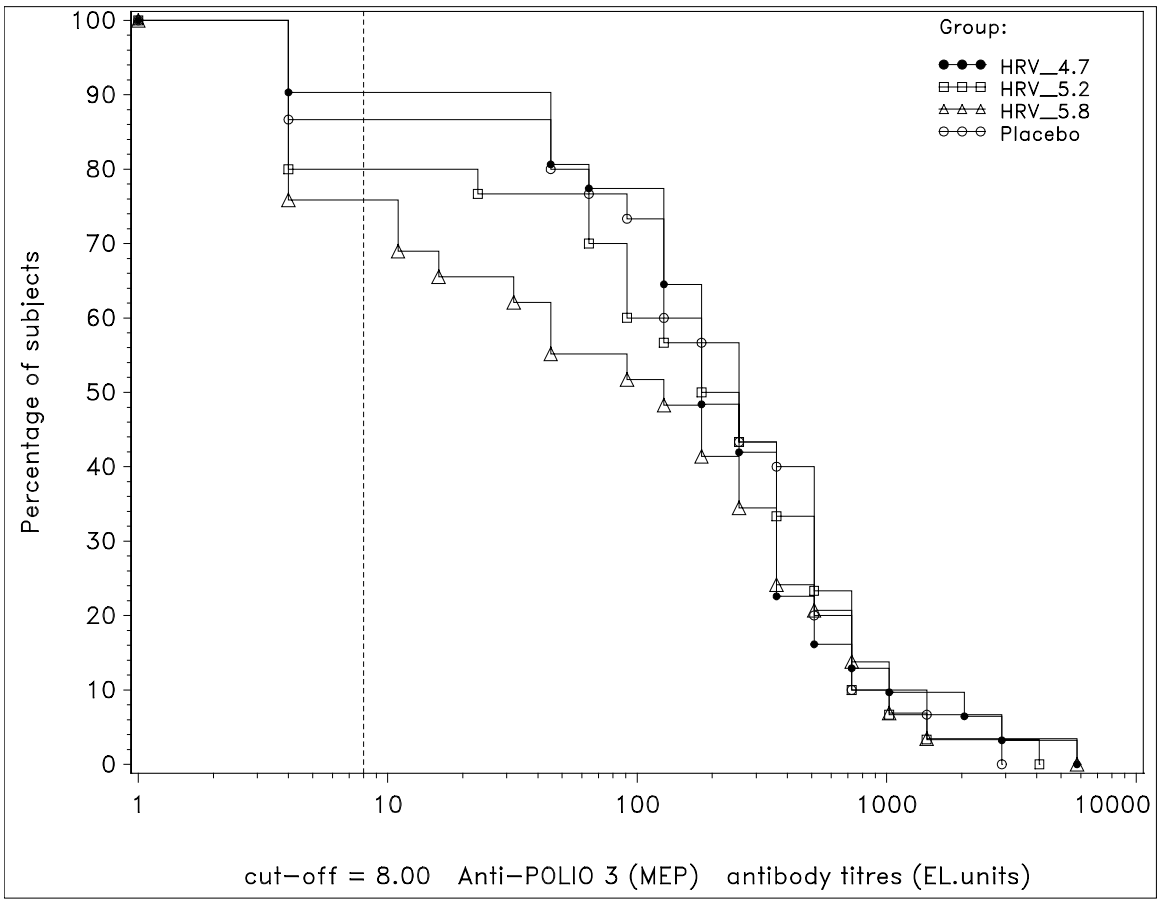
Supplement 186: Reverse cumulative curves for anti-poliovirus type 1 antibody titers two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



Supplement 187: Reverse cumulative curves for anti-poliovirus type 2 antibody titers two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



Supplement 188: Reverse cumulative curves for anti-poliovirus type 3 antibody titers two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



Appendix A: Clintrial Eligibility Codes

Elimination from ATP analysis of safety, immunogenicity and efficacy

1010 Subject or vaccine number not allocated
HRV vaccine or placebo not administered at all
No subject allocated to the randomized number

1030 Study vaccine dose not administered but subject number allocated
HRV vaccine or placebo not administered at all

1040 Administration of vaccine(s) forbidden in the protocol

1050 Randomization failure
Replacement vial used in double-blind studies in with replacement dose are unique whatever the vaccine group
Wrong vaccine vial given
Subject number not in the randomization list and not requested by the sponsor (extra subject)

1060 Randomization code broken at the investigator site (for double-blind studies)

1070 HRV or placebo dose not administered according to protocol

1080 Essential data missing
Date of vaccination unknown
No information on solicited or unsolicited symptoms available: all is missing

1500 Initially positive or unknown status for rotavirus on the day of Dose 1

Elimination from ATP analysis of immunogenicity

2010 Protocol violation (any inclusion/exclusion criteria not met at study entry)
Ex : Demographics - Too young
Too old
Unknown age
Underlying medical condition forbidden by the protocol at screening / Medical history

2040 Administration of any medication forbidden by the protocol

2050 Underlying medical condition forbidden by the protocol during the study

2060 Concomitant infection by rotavirus which may influence immune response

2070 Concomitant infection not related to the vaccine which may influence immune response

2080 Non compliance with vaccination schedule (including wrong and unknown dates)
Not assigned if code 2100 or 2110 has been assigned

2090 Non compliance with blood sample schedule (including wrong and unknown dates)
Not assigned if code 2100 or 2110 has been assigned

2100 Essential serological data missing
Essential blood sample lost
Essential blood sample unable to test (hemolysis, insufficient volume, ...)
Essential blood sample not done
Absence of parallelism

2110 Essential serological data temporarily missing because of not yet tested (interim analysis)

2120 Obvious incoherence, abnormal serology evolution or error in data (incoherence between CRF and results)
Wrong labeling in BS

2130 Subject not planned in the protocol to be bled for their all blood sampling visits (and effectively not bled)

2500 Others

Elimination from ATP analysis of Efficacy

3010 At least one study vaccine dose not administered

3020 Subjects not entered into the surveillance period of the first efficacy follow-up period

3030 Concomitant infection by rotavirus up to 2 weeks after Dose 2 which may influence efficacy response

Appendix B: Mathematical details about the computation of the 95%CI for vaccine efficacy*

The Vaccine Efficacy (VE) can be estimated by:

$$VE = 1 - \frac{n1/N1}{n2/N2} = 1 - \frac{n1}{r * n2}$$

where n1 = number of cases in the vaccine group
N1 = number of subjects in the vaccine group
n1 = number of cases in the placebo group
N2 = number of subjects in the placebo group
r = $\frac{N1}{N2}$

Conditionally to the total number of cases n = n1+ n2 and r, let *p* denote the proportion of cases in the vaccine group,

$$VE = 1 - \frac{n1}{n} * \frac{n}{r * (n - n1)} = 1 - p * \frac{1}{r * (1 - p)} = 1 - \frac{p}{r * (1 - p)}$$

where $p = n1/n$ is binomially distributed

There is therefore a monotonic link between VE, the true vaccine efficacy, and p, the true proportion of subjects in the vaccine group among the total cases in the two groups.

95%CI for vaccine efficacy can then be derived from the exact 95% CI from p.

** V. Dragalin, V. Fedorov and B. Cheuvart. Statistical approaches to establishing vaccine safety. Statistics in medicine 2002; 21:877-893.*

Appendix C: Laboratory Assays

Description of Clinical Immunological Assays

Measurement of IgA Antibodies by ELISA

This assay allows detection of rotavirus IgA in human serum and was initially designed up by R. Ward [7,8] and adapted by SB Bio. It will be used for estimating the immune response after vaccination and/or infection. Samples will be analyzed in SB Biologicals' in Rixensart, Belgium and/or Dr. [redacted] laboratory in Cincinnati, Ohio.

Description of the ELISA Assay

IgG to rotavirus purified from rabbit serum by affinity chromatography (Pierce Immunopure IgG Purification Kit) captures rotavirus antigen on the solid phase. Rabbit serum, obtained from five rabbits or equivalent, immunized with purified rotavirus, is coated on microplate wells at a ad-hoc concentration (100µl/well). After overnight incubation, the wells are washed and coated antibodies are reacted with either MA104 cell lysate infected with 89-12 strain or equivalent (positive wells) or uninfected MA104 cell lysate or equivalent (negative wells), at 50µl/well ad-hoc concentration. Following incubation on a rotating platform (60 minutes, 37°C), the plates are washed and the dilutions of serum samples or standard are incubated in both kinds of wells (positive and negative) (50µl/well). The use of negative wells allows the assessment of the background for each sample (non-specific binding).

During the reaction time (60 minutes, 37°C under agitation), immunoglobulins to rotavirus are captured by bound viral lysate. The plates are washed and human IgA is detected by addition of biotinylated rabbit anti-human IgA at an optimal concentration (50µl/well, 30 minutes at 37°C under agitation). After washing the plates, 50µl of peroxidase-conjugated avidin at an optimal concentration is added to each well and incubated (30 minutes, RT under agitation). Plates are again washed and 50µl of ad-hoc concentration of orthophenylenediamine (OPD) are added per well. The plates are then incubated (30 minutes, room temperature (RT) in darkness) before the reaction is stopped with 100µl/well of 2N H_2SO_4.

Coloration is measured at 490 nm. Specific optical densities are calculated for each sample / standard by measuring the difference between positive and negative wells. Specific optical densities of the standard dilutions generate a standard curve using a 4-parameter logistic function. The four-parameter logistic function describes with a high degree of accuracy a standard curve displaying a pronounced sigmoidal shape when plotted on an optical density-versus-log concentration scale. Concentration of the samples is determined by interpolation of OD values on a defined region of the standard curve. In order to use the most accurate part of the standard curve for the calculation of the results, a range of acceptable OD is defined: acceptable test sample ODs must lie between two specified percentages of the upper limit of the standard curve. Antibody concentration in units per milliliter (U/ml) is determined relative to the standard (concentration=1000U/ml) by averaging the values for each unknown that fall within the working range of the standard curve and then correcting for the dilution factor. Each experiment includes negative and positive controls.

Antigen Detection in Stool Samples

The rotavirus antigen (ROTA Ag) assay detects the presence of ROTA Ag in stool samples. As the small intestine is the site of rotavirus infection, the vaccine must reach this site in order to elicit an immune response. Presence of vaccine / virus in the intestine, indicating a productive infection, may be detected by the ROTA Ag assay. Stool samples are collected from the subjects; suspensions of the stools are tested with the assay. If there is shedding of the vaccine virus in case of undetectable serum IgA, then the subject will be considered as a responder (i.e. vaccine take). Additionally, the test may be used for detecting rotavirus infection associated with gastroenteritis episodes.

The assay designed by R. Ward et al. [**7**,8] was used as the basis for the current SBBio assay method.

Description of the Antigen Detection Assay

Rabbit IgG (DAKO B218), raised against a pool of purified human group A rotaviruses or equivalent, is coated on microplates (positive wells) (100µl/well of an optimal concentration). As control (measurement of background), different wells are coated with non-specific purified Rabbit IgG Fraction (Normal) (DAKO X903) or equivalent (negative wells) (100µl/well of a determined concentration). After an overnight incubation at 4°C, plates are washed and stool suspensions (50µl/well) of the unknown and reference samples are incubated in both kinds of wells. Following incubation on a rotating platform (60 minutes, 37°C), the wells are washed and blocked with 50µl of an optimal concentration of a normal goat serum (15 minutes, RT). Then, guinea-pig antibody (50µl, ad-hoc concentration) to purified double-layered human rotavirus (Wa strain) or equivalent is added for 30 minutes incubation at RT to detect bound ROTA Ag.

After washing the plates, guinea pig antibody specifically fixed on the wells is detected by addition of an optimal concentration of a biotinylated goat anti-guinea-pig immunoglobulin or equivalent (50µl/well) for 30 minutes at RT).

The plates are again washed and 50µl/well of an optimal concentration of peroxidase-conjugated avidin or equivalent are added and incubated (30 minutes, RT). The wells are washed and 50µl of ad-hoc concentration of OPD or equivalent is added per well. After an incubation step of 15 minutes at RT in darkness, the reaction is stopped with 100µl/well of 2N H_2SO_4. Coloration is measured at 490 nm.

A ratio is calculated for each sample (positive well/negative well); the ratio is compared to a threshold. Samples whose ratios are found above the threshold are considered positive while samples with ratios lower than the threshold are considered negative. Each experiment includes a positive reference sample.

Antigen Detection in GE Stool Samples

A rapid screening will be performed at the study sites to determine the presence of rotavirus in the stool using a commercial test (Rotaclone or equivalent). Additional testing for other pathogens is done on rotavirus positive GE stool samples during the first year of efficacy follow-up, but not during the second efficacy follow-up ***period***, as described in section 5.5.2. (amended: 12-FEB-2001) (amended: 26 March 2003) **(amended: 21 August 2003)**

The Reverse Transcriptase Polymerase Chain Reaction Method

Detection of Rotavirus by PCR in Stool Samples

The confirmation of rotavirus from clinical samples will be performed by using the RT-PCR method.

This particular RT-PCR uses primers which in a first round of amplification generate a full length copy of the VP7 gene from any group A rotavirus strain, as described by Gouvea et al.[20].

The first amplification is performed with the primer pair Beg9 and End9. The reaction produces a DNA fragment of 1063 bp length which is visualized on an ethidium bromide-stained agarose gel.

Typing of Rotavirus Polymerase Chain Reaction

The typing of rotavirus from clinical samples will be performed by a second round of amplification.

The typing PCR uses a cocktail of primers specific to the VP7 gene to generate PCR fragments of different sizes specific for G1, G2, G3, G4, and G9 types, as described by Gouvea et al. [20].

The typing PCR is performed with a pool of type-specific primers aBT1, aCT2,aET3, aDT4, aFT9 (variable regions of VP7 gene) that anneals to the 5' end of the VP7 gene and a common primer RVG9 that anneals to the 3'end.

The amplification reaction produces a fragment length characteristic for each type which is visualized on ethidium bromide-stained agarose gel.

Differentiation of G1 Vaccine Strain From G1 Wild Type Strain

To differentiate G1 vaccine strain RIX4414 from G1 wild-type strains, different approaches can be envisaged using the G1 VP7 gene fragment generated by the RT-PCR typing assay (by Slot Blot hybridization , by sequencing).

SAE Narratives

SAE Table

This section contained patient narratives which are textual descriptions of medical history, treatment and outcome for individual patients who experienced a clinically important adverse event including serious adverse events during the trial. They have been excluded to protect patient privacy. This data may be made available subject to an approved research proposal and a determination of the ability to provide information from the specific narratives whilst protecting the patient's privacy. For further information please see the Patient Level Data section of the ***GSK Clinical Study Register****.*

Appendices
Study Information

Protocol Amendment 7 (incl. SIS-IC)

GlaxoSmithKline
Diretoria Médica - Pesquisa Clinica - II Andar
Estrada Dos Bandeirantes, 8464
Jacarepagua
CEP: 22783-110
Rio de Janeiro, Brazil (amended: 11-DEC-2001)

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification 1	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Date of amendment 3	May 3, 2002
Date of amendment 4	July 11, 2002
Date of amendment 5	September 20, 2002
Date of amendment 6	26 March 2003
Date of amendment 7	**21 August 2003**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Medical Monitor (Brazil)

[redacted] M.D.
GSK Jacarepaguá ([redacted])
Estrada dos Bandeirantes 8464 - Jacarepaguá
Rio de Janeiro - RJ
Brasil
CEP 22783-110
Phone: [redacted]
Fax: [redacted]
(amended: 11-DEC-2001) (amended: 26 March 2003)

Clinical Study Director

[redacted] M.D.
GlaxoSmithKline
Diretoria Médica - Pesquisa Clinica - II Andar
Estrada Dos Bandeirantes, 8464
Jacarepagua
CEP: 22783-110
Rio de Janeiro, Brazil
Tel: [redacted]
Fax: [redacted]
(amended: 11-DEC-2001)

This protocol was developed based upon Version 11.2 of SmithKline Beecham Biologicals' Standard Protocol Template.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

(Principal) Investigators Dr. [redacted]
Brazil

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the clinical study as described and will adhere to the Ethical and Regulatory Considerations stated. I have read and understood the contents of the Investigator Brochure.

Signature Date

(Principal) Investigator name

GlaxoSmithKline
Calzada Mexico Xochimilco N° 4900
2d piso
Colonia San Lorenzo Huipulco
Delegacion Tlalpan
CP 14370, Mexico D.F. (amended: 11-DEC-2001)

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification 1	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Date of amendment 3	May 3, 2002
Date of amendment 4	July 11, 2002
Date of amendment 5	September 20, 2002
Date of amendment 6	26 March 2003
Date of amendment 7	**21 August 2003**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Medical Monitor (Mexico)

[redacted] M.D.
GlaxoSmithKline
Calzada Mexico Xochimilco N° 4900
2d piso
Colonia San Lorenzo Huipulco
Delegacion Tlalpan
CP 14370, Mexico D.F.
Tel: [redacted]
Fax: [redacted]
(amended: 11-DEC-2001)
(amended: 11-JULY-2002)

Clinical Study Director

[redacted] M.D.
GlaxoSmithKline
Diretoria Médica - Pesquisa Clinica - II Andar
Estrada Dos Bandeirantes, 8464
Jacarepagua
CEP: 22783-110
Rio de Janeiro, Brazil
Tel: [redacted]
Fax: [redacted]
(amended: 11-DEC-2001)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

(Principal) Investigator Dr. [redacted] Mexico

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the clinical study as described and will adhere to the Ethical and Regulatory Considerations stated. I have read and understood the contents of the Investigator Brochure.

Signature Date

(Principal) Investigator name

GlaxoSmithKline Venezuela ~~Beecham Colombia~~
Calle La Guarita Edf. Los Frailes. Piso 3
Chuao / Caracas
Venezuela (amended: 12-FEB-2001) (amended: 26 March 2003)

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification 1	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Date of amendment 3	May 3, 2002
Date of amendment 4	July 11, 2002
Date of amendment 5	September 20, 2002
Date of amendment 6	26 March 2003
Date of amendment 7	**21 August 2003**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Medical Monitor (Venezuela)

Dr. [redacted]
SmithKline Beecham Venezuela
Calle La Guarita Edf. Los Frailes. Piso 3
Chuao / Caracas
Venezuela
Tel: [redacted]
Mobile: [redacted]
(modified: 14-MAY-2001)
(amended: 11-JULY-2002)

Clinical Study Director

[redacted] M.D.
GlaxoSmithKline
Diretoria Médica - Pesquisa Clinica - II Andar
Estrada Dos Bandeirantes, 8464
Jacarepagua
CEP: 22783-110
Rio de Janeiro, Brazil
Tel: [redacted]
Fax: [redacted]
(amended: 11-DEC-2001)

(Principal) Investigator

Dra. [redacted] M.D.
[redacted]
Venezuela (modified: 14-MAY-2001)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the clinical study as described and will adhere to the Ethical and Regulatory Considerations stated. I have read and understood the contents of the Investigator Brochure.

Signature Date

(Principal) Investigator name

Synopsis

Title

A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Indication

Two dose vaccination against human rotavirus. A subset of subjects (target N = 200) will receive a third dose of the HRV vaccine at 6 months of age. (amended: 3-MAY-2002)

Study Population

Healthy infants 2 months (6 - 12 weeks) of age at time of dose 1

Rationale

This is a dose exploration study to assess the efficacy, reactogenicity, safety and immunogenicity of two doses of the candidate vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in the target age group (infants approximately 2 months of age and previously uninfected with human rotavirus) and receiving concomitant administration of routine vaccinations (i.e. diphtheria and tetanus toxoids and whole-cell pertussis [DTPw], *Haemophilus influenzae* type b [Hib] and Hepatitis B vaccine). Oral polio vaccination will be given at the discretion of the investigator, but should not be administered during the period starting 2 weeks before each dose of study vaccine and ending 2 weeks after. (amended: 12-FEB-2001)

The main objective of this study is to evaluate the efficacy of the study vaccine to prevent any rotavirus gastroenteritis. Protective efficacy will be evaluated in all enrolled subjects until they reach one year of age. Efficacy during a second efficacy follow-up period will be evaluated in a subset of children (about 1000). This study will also

contribute to dose selection and assess the immune response to concomitantly administered routine vaccinations (DTPw-HB+Hib vaccine). (amended: 12-FEB-2001) (amended: 17-SEP-2002) (amended: 26 March 2003) **(amended: 21 August 2003)**

A third dose of the HRV vaccine will be administered to a sub-group of approximately 200 infants in order to explore whether a 3-dose schedule can lead to a higher immune response. (amended: 3-MAY-2002)

Objectives

Primary

For the subset of subjects who receive two doses of HRV or placebo (N=2076). (amended: 3-MAY-2002)

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' HRV vaccine, to demonstrate the efficacy of two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations in preventing any rotavirus gastroenteritis* during the period starting from 2 weeks after dose 2 until the end of the first efficacy follow-up period. (amended: 12-FEB-2001) (amended: 20-SEP-2002)

Rotavirus gastroenteritis for efficacy analysis is defined as a episode of gastroenteritis (diarrhea), occurring at least two weeks after dose 2 in which rotavirus other than vaccine strain is identified in a stool sample collected within 7 days after the onset of gastroenteritis symptoms.

Secondary (amended: 3-MAY-2002) (amended: 20-SEP-2002)

Efficacy

First year follow-up

For the subset of subjects who receive two doses of HRV or placebo (N=2076):

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' HRV vaccine, to assess if two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations can: (amended: 12-FEB-2001)
  - ♦ Prevent severe rotavirus gastroenteritis during-the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
  - ♦ Prevent rotavirus gastroenteritis due to virus types heterologous to vaccine strain from two weeks after dose 2 until the end of the first efficacy follow-up period. (amended: 12-FEB-2001)
  - ♦ Prevent any and severe pure rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
  - ♦ Prevent mixed rotavirus gastroenteritis (gastroenteritis associated with rotavirus and at least one other pathogen) during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
  - ♦ Prevent any hospitalization for rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period (see section 8.5.1 for definition of hospitalization).

For the subset of subjects who receive three doses of HRV or placebo (N~200):

- To explore the rates of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the first efficacy follow-up period.

Second follow-up ***period*** *(for a subset of about 1000 subjects)*

- To evaluate the efficacy of the HRV vaccine during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period, and during the period starting from 2 weeks after the last HRV/placebo dose

until the end of the second efficacy follow-up period.

The endpoints evaluated for this second ***follow-up period*** analysis (severity and nature of disease, study groups and subsets) will be similar to those evaluated during the first year of follow-up (refer to section 10.5.4 for details).

(amended: 21 August 2003)

Immunogenicity

For the subset of subjects who receive two doses of HRV or placebo (N=2076):

- To assess vaccine take, in subjects previously uninfected with rotavirus before vaccination, two months after each study vaccine dose in a subset of 800 subjects. Take is defined as the appearance of serum IgA to rotavirus in post-immunization sera at a titer ≥ 20 U/ml or vaccine virus shedding in any stool sample collected from Visit 1 to Visit 3. (amended: 12-FEB-2001)
- To assess persistence of serum IgA to rotavirus at the end of the first efficacy follow-up period.
- To explore in a subset of 800 subjects the effect of SB Biologicals' rotavirus vaccine on the immune response to concurrently administered routine vaccinations. (amended: 12-FEB-2001)
- To explore the effect of unrestricted feeding on the immunogenicity of the vaccine.
- To assess viral shedding in the vaccine groups in a subset. (amended: 12-FEB-2001)

Note: the immunogenicity/stool subset is described in section 6.4. (amended: 12-FEB-2001)

For the subset of subjects who receive three doses of HRV or placebo

(N~200):

- To assess serum IgA to rotavirus, two months after dose 2 and dose 3 of study vaccine or placebo.
- To assess viral shedding in the vaccine groups after the third HRV vaccine dose.
- To explore the effect of SB Biologicals' rotavirus vaccine on the immune response to concurrently administered routine vaccinations two months after the third dose of routine vaccines.

Safety/Reactogenicity

- To assess the safety and reactogenicity of two doses of SB Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo. (amended: 12-FEB-2001)
- To assess the safety and reactogenicity of the third dose of SB Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo in a subset of subjects (N~200). (amended: 3-MAY-2002)

Refer to Glossary of Terms for definition of term used.

Study design

- Experimental design: Double-blind, randomized, placebo-controlled, with four parallel groups.

Group A: HRV ($10^{4.7}$ ffu) vaccine.
Group B: HRV ($10^{5.2}$ ffu) vaccine.
Group C: HRV ($10^{5.8}$ ffu) vaccine. (amended: 12-FEB-2001)
Group D: Placebo.

- Treatment allocation: Randomized with balanced allocation (1:1:1:1). Refer to section 6.4 for randomisation method.
- Indication: Two oral doses will be administered to healthy infants who are 2 months of age at the time of dose 1.

A subset of subjects (target N = 200) will receive a third dose of

the HRV vaccine. (amended: 3-MAY-2002)

- All subjects will be followed for efficacy until one year of age and a subset, about 1000 subjects, will be followed for efficacy until ***a maximum of*** two years of age. (amended: 20-SEP-2002) **(amended: 21 August 2003)**
- Blinding: double-blind for HRV vaccine and placebo. The parents/guardians of the subjects and the study personnel will be blinded to the treatment administered. Blinding will be maintained for the whole study period. Refer to section 6.5. (amended: 3-MAY-2002)
- Control: Placebo.
- Study will be conducted independently in Brazil, Mexico and Venezuela. In each country the local responsibility for directing, monitoring and supporting the study will belong to the local SB units medical staff.
- For the subjects who participate only in the first year of efficacy follow-up (until age 12 months), the intended duration of the study, per subject, will be approximately 10 months for subjects. For the subset of subjects who participate in ***the*** second efficacy follow-up ***period*** (until ***maximum*** age 24 months), the intended duration of the study, per subject, will be 22 months ***at most***. (amended: 20-SEP-2002) (amended: 26 March 2003) **(amended: 21 August 2003)**

Study Procedures

- Hepatitis B, BCG and OPV vaccination at birth is allowed according to local Expanded Program of Immunization (EPI) [should be documented in the electronic Case Report Form (eCRF)].
- Routine vaccinations (DTPw-HB+Hib vaccine) should be administered concomitantly with the study vaccines at 2 and 4 months of age; thereafter, DTPw-HB+Hib vaccine will be given at 6 months of age. Oral polio vaccination will be given at the discretion of the investigator, but should not be administered

during the period starting 2 weeks before each dose of study vaccine and ending 2 weeks after. Routine vaccinations, including OPV, must be documented in the eCRF.

- There will be no restrictions on feeding the infants before or after study vaccines' administration.
- Study visits:

Visit 1 (2 Months of Age) – Pre-vaccination blood sample from all subjects, Dose 1 of study vaccine or placebo and Dose 1 of routine vaccinations (i.e. DTPw-HB+Hib).

Visit 2 (4 Months of Age) – Blood sample in a subset (800 subjects), Dose 2 of study vaccine or placebo and Dose 2 of routine vaccinations (DTPw-HB+Hib vaccine). (amended: 12-FEB-2001)

Visit 3 (6 Months of Age) – Blood sample in a subset (800 subjects) and Dose 3 of routine vaccinations (DTPw-HB+Hib vaccine). (amended: 12-FEB-2001).

Study visit at the end of the first year of efficacy follow-up (1 Year of Age) – Blood sample from subjects who receive two doses of study vaccine or placebo, and Efficacy Follow-up. This will be the final study visit for the subjects who participate only in the first year of efficacy follow-up. (amended: 3-MAY-2002) (amended: 20-SEP-2002)

A subset of subjects (N ~ 200) enrolled in Brazil will receive a third dose of the HRV vaccine or placebo along with blood sampling at Visit 3. A study visit (Visit 4) will take place for these subjects two months after the third dose of study vaccine or placebo to collect a blood sample. For these subjects the first year of efficacy follow-up study visit will take place at approximately one year of age: a blood sample will not be taken from this subset at this visit. (amended: 3-MAY-2002) (amended: 20-SEP-2002) (amended: 26 March 2003)

Study visit at the end of the second efficacy follow-up ***period*** (24 months of age maximum) – Efficacy Follow-up. This will be the final study visit for the subjects who participate in a second efficacy

follow-up ***period***. (amended: 3-MAY-2002) (amended: 20-SEP-2002) (amended: 26 March 2003) **(amended: 21 August 2003)**

- Active follow-up for safety and gastroenteritis via weekly visit to a subject by study personnel (Health Worker) starting 1 week after dose 1 and ending at the study visit at the end of the second efficacy follow-up period. For the subjects who participate only in the first year of efficacy follow-up, active follow-up for safety and gastroenteritis via weekly visit to a subject by study personnel (Health Worker) will end at the study visit at the end of the first efficacy follow-up period. (amended: 3-MAY-2002) (amended: 20-SEP-2002)
- 15-day follow-up period (day 0 to day 14) on solicited symptoms (fever, fussiness / irritability, diarrhea, vomiting, loss of appetite and cough/runny nose) after any dose of study vaccine using diary cards (in a subset of approximately 200 subjects after dose 3). (amended: 3-MAY-2002)
- Blood samples will be drawn from all subjects at study Visits 1, from subjects receiving two doses of study vaccine or placebo at the end of the first efficacy follow-up period and in a subset (N = 800) at Visits 2 and 3. Blood samples will be drawn from the subset receiving three doses of study vaccine or placebo (N ~ 200) at Visit 3 (two months after dose 2) and Visit 4 (two months after dose 3). (amended: 3-MAY-2002) (amended: 20-SEP-2002)
- Stool samples will be collected from a subset of 400 subjects enrolled on the day of administration of dose 1 and dose 2 and on day 7 following each dose of study vaccine (amended: 12-FEB-2001). Stool samples will be collected from the subset receiving three doses of study vaccine/placebo (N ~ 200) on the day of administration of dose 3 and on day 7 following dose 3 of study vaccine. (amended: 3-MAY-2002)
- Recording of unsolicited symptoms within 42 days after dose 1, dose 2 (in all subjects), and dose 3 (in a subset of approximately

200 subjects) of the study vaccines. (amended: 3-MAY-2002)

- Recording of serious adverse events throughout the study period.
- Data collection will be by remote data entry.
- Recruitment time will be discussed in the recruitment plan, which is summarised in Appendix C.
- Information on feedings on the day of each study vaccine administration will be recorded for all subjects. The parent/guardian will be questioned whether the child is fed with breast milk or infant formula and whether the child was fed within 60 minutes before vaccination and/or within 30 minutes after vaccination.
- For each suspected gastroenteritis episode occurring from day of dose 1 until study end, a stool sample will be collected as soon as possible after the onset of gastroenteritis and will be brought as soon as possible to the study site. A second stool specimen will be collected if the first stool sample was not sufficient. (amended: 12-FEB-2001)
- All stool samples collected during gastroenteritis episodes will be refrigerated upon receipt by Study Personnel. A portion of the sample will be tested by Rota Ag ELISA to determine the presence of rotavirus. All positive samples will be tested by PCR to determine G type. If any G1 rotavirus is detected in the stool specimens between Visit 1 and Visit 3 (Visit 4 for the subset receiving three doses of study vaccine or placebo), vaccine virus will be differentiated from the wild type serotype by sequence analysis or an equivalent approach. In addition, rotavirus positive stool samples will be cultured locally to determine the presence/absence of mixed infections. (amended: 3-MAY-2002)
- As part of a site-specific sub-study in Venezuela, stool samples, up to a maximum of 10 over the study period, will be collected from a subset of 200 subjects enrolled in Venezuela. Also, two additional stool samples will be collected from this subset during

each gastroenteritis episode occurring during the study period. (amended: 10-OCT-2001)

Number of subjects

Target enrollment was planned at 2640 (660 subjects in each group) to obtain 2360 evaluable subjects (590 each group) for the analysis of the primary objective.

However, the target sample could not be reached because of difficulty in enrolling eligible subjects for participation in the study. The final enrollment is 2276 eligible subjects. (amended: 3-MAY-2002)

Primary endpoint

For the subset of subjects who receive two doses of HRV or placebo (N=2076). (amended: 3-MAY-2002)

- Occurrence of any rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the first efficacy follow-up period. (amended: 20-SEP-2002)

Secondary endpoints

(amended: 3-MAY-2002) (amended: 20-SEP-2002)

Efficacy

For the subset of subjects who receive two doses of HRV or placebo (N=2076).

- Occurrence of severe rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
- Occurrence of rotavirus gastroenteritis due to virus types heterologous to vaccine strain during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period. (amended: 12-FEB-2001)
- Occurrence of any and severe pure rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
- Occurrence of rotavirus gastroenteritis in which there is at least

one other pathogen during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.

- Occurrence of hospitalization for rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.

For the subset of subjects who receive three doses of HRV or placebo (N~200):

- Occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the first efficacy follow-up period.

For the subset of subjects who participate in a second efficacy follow-up ***period*** (until ***maximum*** age 24 months): (amended: 26 March 2003) **(amended: 21 August 2003)**

- For the subset of subjects who receive two doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.
- For the subset of subjects who receive two doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the second efficacy follow-up period.
- For the subset of subjects who receive three doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.
- For the subset of subjects who receive three doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the second efficacy follow-up period.

Immunogenicity endpoints

For the subset of subjects who receive two doses of HRV or placebo (N=2076).

- Serum rotavirus IgA antibody titers at Visit 1 and the end of the first efficacy follow-up period visit and at Visits 2 and 3 in a subset (N=800).
- Proportion of subjects with vaccine take at visits 2 and 3 in a subset (N=800).
- Vaccine take and GMTs of rotavirus IgA ELISA will be calculated in a subset for breast fed infants compared with formula fed infants for the following 3 categories: 1) whether the infant received no food 1 hour prior to and 30 minutes after dose 1 or dose 2 (as reported by the mother); 2) whether the infant received food 1 hour prior to dose 1 or dose 2 (as reported by the mother); and 3) whether the infant received food within 30 minutes after dose 1 or dose 2.
- Viral shedding in the vaccine groups in a subset (N = 400).

Two months after dose 2 (at Visit 3) and at year 1 ~~(at final study visit)~~ in a subset (800 subjects). (amended: 12-FEB-2001)

- GMTs for anti-PRP, anti-diphtheria and anti-tetanus toxoids, anti-BPT, anti-polio type 1, 2 and 3 and anti-HBs.
- Seroprotection status:
  - ◊ anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
  - ◊ anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-HBs antibody concentrations ≥ 10.0 mcg/ml
  - ◊ anti-polio type 1 antibody titers ≥ 8
  - ◊ anti-polio type 2 antibody titers ≥ 8
  - ◊ anti-polio type 3 antibody titers ≥ 8
- Seropositivity status:

◊ anti-BPT antibody concentrations ≥ 15 EL.U/ml

For the subset of subjects who receive three doses of HRV or placebo (N~200):

- Serum rotavirus IgA antibody titers at visit 1, 3 and 4.
- GMTs for anti-PRP, anti-diphtheria and anti-tetanus toxoids, anti-BPT, anti-polio types 1, 2 and 3 and anti-HBs, two months after dose 3.
- Seroprotection status two months after dose 3:
  - ◊ anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
  - ◊ anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-HBs antibody concentrations ≥ 10.0 mcg/ml
  - ◊ anti-polio type 1 antibody titers ≥ 8
  - ◊ anti-polio type 2 antibody titers ≥ 8
  - ◊ anti-polio type 3 antibody titers ≥ 8
- Seropositivity status two months after dose 3:
  - ◊ anti-BPT antibody concentrations ≥ 15 EL.U/ml
- Viral shedding in the vaccine groups on the day of and on day 7 after dose 3.

Safety endpoints

- For each type of solicited symptoms, occurrence of the symptom within the 15-day solicited follow-up period after any dose of study vaccine (in a subset after dose 3).
- Occurrence of unsolicited symptoms within 42 days after dose 1, dose 2 (in all subjects) and dose 3 (in a subset), according to WHO classification.
- Occurrence of serious adverse events throughout the entire study period

Analyses

The final analysis will be performed at the end of the first efficacy follow-up period, after all enrolled subjects have completed the study visit at the end of the first follow-up period. Analysis of data

collected during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be presented in an annex. (amended: 20-SEP-2002)
Two interim analyses will be performed on immunogenicity and reactogenicity of the vaccines to provide early information on dose selection of phase III studies. The interim results will be limited to summaries by group. (amended: 12-FEB-2001)
Two interim analysis on efficacy against any and severe rotavirus gastroenteritis will be performed to obtain early efficacy data. (amended: 11-JULY-2002) (amended: 26 March 2003)
The results of all interim analyses may be presented at scientific conferences and, as required, to the authorities. (amended: 3-MAY-2002) (amended: 11-JULY-2002)

Definitions

Diarrhea: Three or more looser than normal stools within a day.

First year of efficacy follow-up period: Each subject will be followed for the efficacy analysis starting from two weeks post dose 2 until the age of approximately one year. (amended: 20-SEP-2002)

Second efficacy follow-up period: approximately 1000 subject will be followed for a second efficacy analysis either until ***October 2003*** (for subjects from Brazil and Venezuela) or until the end of the 2003 rotavirus season (for subjects from Mexico) (amended: 26 March 2003) **(amended: 21 August 2003)**

Gastroenteritis: Diarrhea.

Two occurrences of gastroenteritis will be classified as separate episodes if there are 5 or more symptom-free days between the episodes.

Mixed rotavirus gastroenteritis: Gastroenteritis associated with rotavirus and at least one other pathogen.

Pure rotavirus gastroenteritis: Rotavirus gastroenteritis with no other concurrent pathogen infection.

Rotavirus gastroenteritis: All rotavirus gastroenteritis (pure and mixed rotavirus gastroenteritis).

Rotavirus gastroenteritis for efficacy analysis: An episode of gastroenteritis (diarrhea) occurring at least two weeks after dose 2 in which rotavirus other than vaccine strain is identified in a stool sample collected not later than 7 days after the onset of gastroenteritis symptoms.

Severe rotavirus gastroenteritis: An episode of rotavirus gastroenteritis with score ≥ 11 on a 20 point scoring system [1].

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Vaccine take: For subjects previously uninfected with rotavirus before vaccination, appearance of serum IgA to rotavirus in post-immunization sera at a titer ≥ 20 U/ml or vaccine virus shedding in any stool sample collected from Visit 1 to Visit 3.

Vomiting: One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

Table of Contents

Page No.

Synopsis 11
1. Introduction 35
   1.1 Human rotavirus 89-12 strain 37
   1.2 Rationale 38
2. Objectives 39
   2.1 Primary objective 39
   2.2 Secondary objectives 39
3. Study Design Overview 42
4. Study Cohort 47
   4.1 Number of subjects / centers 47
   4.2 Inclusion criteria 48
   4.3 Exclusion criteria 48
   4.4 Elimination criteria during the study up to Visit 3 (up to Visit 4 for the subset of 200 subjects receiving three doses of study vaccine/placebo) 49
   4.5 Elimination criteria during the study from Visit 3 (from Visit 4 for the subset of 200 subjects receiving three doses of study vaccine/placebo) until the study end (amended: 3-MAY-2002) (amended: 20-SEP-2002) 50
   4.6 Contraindications to vaccination 51
5. Conduct of Study 52
   5.1 Ethics and regulatory considerations 52
      5.1.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC) 53
      5.1.2 Informed consent 54
   5.2 General study aspects 56
   5.3 Outline of study procedures 58
   5.4 Detailed description of study stages/visits 62
   5.5 Sample handling and analysis 73
      5.5.1 Treatment and storage of biological samples 73
      5.5.2 Laboratory assays 73
      5.5.3 Serology plan 76
6. Study Vaccine(s) and Administration 78
   6.1 Study vaccine(s) 78
      6.1.1 SmithKline Beecham Biologicals' HRV vaccine 78
      6.1.2 Placebo 79

6.1.3 SmithKline Beecham Biologicals' $CaCO_3$ buffer 79
6.1.4 Commercial EPI vaccines 80
6.2 Dosage and administration 80
Injection technique 81
6.3 Storage 82
6.4 Treatment allocation and randomisation 82
6.5 Method of blinding and breaking the study blind 84
6.6 Replacement of unusable vaccine doses 84
6.7 Packaging 85
6.8 Vaccine accountability 85
6.9 Concomitant medication/treatment 85
7. Health Economics 86
8. Adverse Events 86
8.1 Eliciting and documenting adverse events 86
8.1.1 Solicited adverse events 89
8.1.2 Surveillance of gastroenteritis 90
8.2 Assessment of intensity 90
8.2.1 Solicited symptoms 91
8.2.2 Unsolicited symptoms 93
8.2.3 Intensity of gastroenteritis episodes for efficacy analysis 93
8.3 Assessment of causality 95
8.4 Following-up of adverse events and assessment of outcome 96
8.5 Serious adverse events 97
8.5.1 Definition of a serious adverse event 97
8.5.2 Reporting serious adverse events 98
8.6 Pregnancy 102
8.7 Treatment of adverse events 102
9. Subject Completion and Drop-out 102
9.1 Definition 102
9.2 Procedures for handling drop-outs 102
9.3 Reasons for drop-out 103
10. Data Evaluation: criteria for evaluation of objectives 103
10.1 Primary endpoint 103
10.2 Secondary endpoints 103
10.3 Study cohorts/data sets to be evaluated 107
10.4 Estimated sample size 109
10.5 Final analyses 112
10.5.1 Analysis of demographics 113

10.5.2 Analysis of safety 113
10.5.3 Analysis of immunogenicity 114
10.5.4 Efficacy analysis 115
10.6 Interim analysis 119
11. Administrative Matters 121
12. References 122
Appendix A: World Medical Association Declaration of Helsinki 125
Appendix B: Administrative Matters 131
Appendix C: Overview of the recruitment plan 139
Appendix D: Handling of Biological Samples Collected by the Investigator 140
Appendix E: Shipment of Biological Samples 144
Appendix F: Laboratory Assays 145
Appendix G: Vaccine Supplies, Packaging and Accountability 150
Appendix H: Sample Subject Information and Informed Consent 153
Appendix I: Follow-up of intussusception cases 170
Appendix J: Mathematical details about sample size determination 173
Appendix L: Site-specific study of rotavirus specific IgA antibodies in feces in Venezuela 174
Appendix M: Supplemental Subject Information and Informed Consent (amended: 3-MAY-2002) 177
Appendix N: Supplemental Subject Information and Informed Consent (amended: 20-SEP-2002) 181
Appendix K: Protocol Amendments/Modifications 185
ANNEX 1 (provided as a separate pdf document): The Standard Verbal Autopsy Questionnaire (amended: 26 March 2003)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

List of Abbreviations

AE	—	Adverse event
AGMK	—	African green monkey kidney
Anti-BPT	—	antibody to pertussis toxoid
Anti-diphtheria	—	antibody to diphtheria toxoid
Anti-polio	—	antibody to polio
Anti-PRP	—	antibody to polyribosyl-ribitol phosphate
Anti-tetanus	—	antibody to tetanus toxoid
AR	—	Attack rate
ATP	—	According-to-protocol
CI	—	Confidence interval
eCRF	—	Electronic Case Report Form
DSMB	—	Data Safety Monitoring Board.
DTPw	—	diphtheria and tetanus toxoids and whole-cell pertussis
ELISA	—	enzyme-linked immunosorbent assay
EPI	—	Expanded Program of Immunization
GE	—	Gastroenteritis
GMT	—	geometric mean antibody titer
Hib	—	*Haemophilus influenzae* type b
HBV	—	Hepatitis B vaccine
HRV	—	Human Rotavirus
IEC	—	Independent Ethics Committee
Ig	—	immune globulin
IRB	—	Institutional Review Board
ml	—	Milliliter
ffu	—	Foci forming units
OPV	—	Oral polio virus
PID	—	Patient identification number
ROTA Ag	—	Rotavirus antigen
SAS	—	Statistical Analysis System
SB	—	SmithKline Beecham
US	—	United States of America
VAERS	—	Vaccine Adverse Event Reporting System

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

VP	—	Viral Protein
WHO	—	World Health Organization

Glossary of Terms

Diarrhea:	Three or more looser than normal stools within a day.
First year of efficacy follow-up period:	Each subject will be followed for the efficacy analysis starting from two weeks post dose 2 until the age of approximately one year. (amended: 20-SEP-2002) (amended: 26 March 2003)
Second efficacy follow-up *period*:	Approximately 1000 subject will be followed for a second efficacy analysis either until ***October 2003*** (for subjects from Brazil and Venezuela) or until the end of the 2003 rotavirus season (for subjects from Mexico) (amended: 26 March 2003) **(amended: 21 August 2003)**
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in analysis (see Section 10.3 for details on criteria for evaluability).
Gastroenteritis:	Diarrhea
Medical Monitor:	An individual medically qualified to assure the responsibilities of the sponsor especially as regards the ethics, clinical safety of a study and the assessment of adverse events.
Mixed rotavirus gastroenteritis:	Gastroenteritis associated with rotavirus and at least one other pathogen.
Pure rotavirus gastroenteritis:	Rotavirus gastroenteritis with no other concurrent pathogen infection

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Rotavirus gastroenteritis	All rotavirus gastroenteritis (pure and mixed rotavirus gastroenteritis).
Rotavirus gastroenteritis for efficacy analysis:	An episode of gastroenteritis (diarrhea) occurring at least two weeks after dose 2 in which rotavirus other than vaccine strain is identified in a stool sample collected not later than 7 days after the onset of gastroenteritis symptoms.
Separate episodes of gastroenteritis:	Two occurrences of gastroenteritis with 5 or more symptom-free days between the episodes.
Severe rotavirus gastroenteritis:	An episode of rotavirus gastroenteritis with score ≥ 11 on a 20 point scoring system [1].

Clinical Study Monitor:	An individual assigned by SmithKline Beecham who is responsible for assuring proper conduct of a clinical study at one or more investigational sites.
Subject(s):	Term used throughout the protocol to denote the enrolled individual(s).
Vaccine take:	For subjects previously uninfected with rotavirus before vaccination, appearance of serum IgA to rotavirus in post-immunization sera at a titer ≥ 20 U/ml or vaccine virus shedding in any stool sample collected from Visit 1 to Visit 3.
Vomiting:	One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

1. Introduction

Rotaviruses, non-enveloped double-stranded RNA viruses, infect both humans and animals, and are distributed worldwide. In humans, rotavirus infection induces a spectrum of symptoms from sub-clinical to mild diarrhea to a severe and occasionally fatal dehydrating illness. Rotavirus is the most important cause of acute gastroenteritis (GE) requiring hospitalization of infants and young children in developed countries and is a frequent cause of death in children less than 5 years of age in developing regions of the world (estimated nearly one million deaths)[2].

Maximal HRV incidence is in infants 6 to 24 months of age, while seroepidemiology and other surveys show that nearly all children have been infected prior to 3 years of age, regardless of country or socioeconomic setting. In developing countries located in the tropics, rotavirus disease occurs year round. In Mexico City, there is a clear seasonal peak which occurs in the winter [22]. More than 90 % of circulating HRV are of G1, G2, G3 and G4 types (based on the outer shell layer viral protein 7 [VP7]). The remainder of the outer layer of the rotavirus particle shell consists primarily of another protein, VP4, which has less variability than VP7.

Natural immunity induced by rotavirus infection protects infants from subsequent episodes of severe disease. Successive encounters with rotaviruses (even of the same serotype) were shown to increase the initial specific immune response while also allowing for expansion of heterotypic immune responses [3,4]. Prevention by vaccine is considered to be critical for HRV, as only non-specific symptomatic therapies are available.

A variety of approaches to the development of rotavirus vaccines have been undertaken, with live oral attenuated candidates receiving the most attention. A major approach has been to generate animal-human rotavirus reassortants that derive the segments encoding VP7 from human rotaviruses, and all other segments from animal virus. Reassortants based on rhesus and bovine strains have been evaluated.

In August 1998, a vaccine based on rhesus monkey strain of G3 serotype plus three rhesus-human reassortants, with G1, G2, and G4 VP7 genes, was licensed in the United States of America (US) under the commercial name RotaShield® by Wyeth-Lederle Vaccines for 3- dose series in infants. It was found that the rhesus monkey rotavirus vaccine, RotaShield®, is associated with an increased risk of intussusception (a rare type of bowel obstruction that occurs when one segment of bowel becomes enfolded within another segment) in the first 1-2 weeks after vaccination with RotaShield®, particularly following the first dose.

Symptoms consistent with intussusception are severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41°C. It is reported that intussusception occurred naturally in 136 out of 269,832 children per year (or 0.05%) in New York state, US from 1991-1995, and in 37 out of 49,999 children (or 0.074%) in Northern California Kaiser Permanente Hospitals, US from 1995-1996 [5].

Active post-licensure surveillance in two states in the US (California and Minnesota) indicated that the observed rate of intussusception among RotaShield® vaccine recipients appears to be greater than expected (45/100,000 infant-years[1] in never-vaccinated children and 125/100,000 infant-years in RotaShield® recipients). Post-licensure statistics also indicated that the rate of intussusception reports was considerably higher in the first seven days after a dose of RotaShield® (314/100,000 infant-years in California and 292/100,000 infant-years in Minnesota). Following licensure of RotaShield® in the US and an estimated administration of approximately 1.5 million doses, 15 cases of intussusception were reported to the Vaccine Adverse Event Reporting System (VAERS) during September 1, 1998 to July 7, 1999. VAERS is a passive surveillance system operated by the Food and Drug Administration (FDA) and Center for Disease control (CDC) [6]. Intussusception was identified as an

[1] An infant-year is a unit of measurement combining infants and time used as a denominator in calculating incidence. Here, it is the sum of the individual units of time (days, weeks or months) converted to years that the infants in the study population have been followed.

uncommon serious adverse event associated with the RotaShield® vaccine and the recommendation to vaccinate with RotaShield® was withdrawn.

Another approach has been to develop attenuated HRV isolates either by passage in cell cultures or as nursery strains. These attenuated viruses are able to replicate well in the human intestine and to trigger local and systemic responses. A potential advantage of this approach over animal rotavirus reassortants is that the immune response is induced against all the components of a human rotavirus, including VP4 and VP6, and not only against VP7. The candidate HRV vaccine being tested in this study is based on a rotavirus strain affecting humans and is different from the rotavirus vaccine that was associated with intussusception.

1.1 Human rotavirus 89-12 strain

The active ingredient in SmithKline Beecham (SB) Biologicals' HRV vaccine candidate is human rotavirus strain 89-12. The 89-12 HRV strain was obtained from the stool of a 15-month old infant with a mild rotavirus diarrhea in December 1988. This 89-12 strain belonging to the serotype G1P1A and genotype (P8). A two-year prospective study showed that natural infection with such strains provided protection against subsequent illness and against re-infection [3].

The initial isolate was passaged in primary African Green Monkey Kidney cells (AGMK), and then further passage on an approved AGMK cell line to produce initial clinical lots of vaccine based on uncloned P33 89-12 HRV strain.

Previous clinical development of the uncloned P33 89-12 strain was done by AVANT Immunotherapeutics, Inc., a biotechnology company in the US (previously called Virus Research Institute (VRI)), under BB-IND 5245 (Human Rotavirus Serotype G1 Vaccine Strain 89-12; AGMK cells, Live Attenuated, Oral). Those studies demonstrated the safety, immunogenicity and feasibility of the uncloned P33 89-12 vaccine candidate in infants [7,8]. A Phase IIb trial demonstrated that two doses of 10^5ffu of uncloned P33 89-12 provided infants 89 % (95% CI, 65.4-94.5%) protection against any GE due to rotavirus, as well as 100% efficacy against

very severe (> 14 points) rotavirus GE during the first rotavirus disease season after vaccination.

SB Biologicals has taken over the manufacturing process and clinical development of the 89-12 vaccine from AVANT. SB Biologicals has implemented several process changes to develop a lyophilised HRV vaccine based on a cloned P43 89-12 HRV strain (referred to as RIX4414).

Four studies (444563/001 in adults, 444563/002 in seropositive toddlers, 444563/003 and 444563/004 in seronegative infants) have been initiated with SB Biologicals' candidate HRV vaccine, RIX4414. So far, the candidate vaccine was safe in all age groups including previously uninfected infants.

Please refer to the Investigator Brochure for a review of information on the HRV vaccine.

1.2 Rationale

This is a dose exploration study to assess the efficacy, reactogenicity, safety and immunogenicity of two doses of the candidate vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu), in the target age group (infants approximately 2 months of age and previously uninfected with human rotavirus). (amended: 12-FEB-2001)

The main objective of this study is to evaluate the efficacy of the study vaccine to prevent rotavirus gastroenteritis. Protective efficacy will be evaluated in all enrolled subjects until they reach one year of age. Efficacy during a second efficacy follow-up period will be evaluated in a subset of children (about 1000). This study will also contribute to dose selection. (amended: 20-SEP-2002) (amended: 26 March 2003) **(amended: 21 August 2003)**

This study will also assess the immune response to concomitantly administered routine vaccinations (DTPw-HB+Hib vaccine).

A third dose of the HRV vaccine will be administered to a sub-group of

approximately 200 infants in order to explore whether a 3-dose schedule can lead to a higher immune response. (amended: 3-MAY-2002)

2. Objectives

2.1 Primary objective

For the subset of subjects who receive two doses of HRV or placebo (N=2076). (amended: 3-MAY-2002)

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' HRV vaccine, to demonstrate the efficacy of two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations in preventing any-rotavirus gastroenteritis* during the period starting from 2 weeks after dose 2 until the end of the first efficacy follow-up period. (amended: 12-FEB-2001) (amended: 20-SEP-2002)

* Rotavirus gastroenteritis for efficacy analysis is defined as a episode of gastroenteritis (diarrhea), occurring at least two weeks after dose 2 in which rotavirus other than vaccine strain is identified in a stool sample collected within 7 days after the onset of gastroenteritis symptoms.

2.2 Secondary objectives

(amended: 3-MAY-2002) (amended: 20-SEP-2002)

Efficacy

First year follow-up

For the subset of subjects who receive two doses of HRV or placebo (N=2076):

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' HRV vaccine, to assess if two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations can: (amended: 12-FEB-2001)

- Prevent severe rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
- Prevent rotavirus gastroenteritis due to virus types heterologous to vaccine strain from two weeks after dose 2 until the end of the first efficacy follow-up period. (amended: 12-FEB-2001)
- Prevent any and severe pure rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
- Prevent mixed rotavirus gastroenteritis (gastroenteritis associated with rotavirus and at least one other pathogen) during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
- Prevent any hospitalization for rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period (see section 8.5.1 for definition of hospitalization).

For the subset of subjects who receive three doses of HRV or placebo (N~200):

- To explore the rates of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the first efficacy follow-up period.

Second follow-up ***period*** *(for a subset of about 1000 subjects)*

- To evaluate the efficacy of the HRV vaccine during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period, and during the period starting from 2 weeks after the last HRV/placebo dose until the end of the second efficacy follow-up period.

  The endpoints evaluated for this second ***follow-up period*** analysis (severity and nature of disease, study groups and subsets) will be similar to those evaluated during the first year of follow-up (refer to section 10.5.4 for details).

(amended: 21 August 2003)

Immunogenicity

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

For the subset of subjects who receive two doses of HRV or placebo (N=2076):

- To assess vaccine take, in subjects previously uninfected with rotavirus before vaccination, two months after each study vaccine dose in a subset of 800 subjects. Take is defined as the appearance of serum IgA to rotavirus in post-immunization sera at a titer ≥ 20 U/ml or vaccine virus shedding in any stool sample collected from Visit 1 to Visit 3. (amended: 12-FEB-2001)
- To assess persistence of serum IgA to rotavirus at the end of the first efficacy follow-up period.
- To explore in a subset of 800 subjects the effect of SB Biologicals' rotavirus vaccine on the immune response to concurrently administered routine vaccinations. (amended: 12-FEB-2001)
- To explore the effect of unrestricted feeding on the immunogenicity of the vaccine.
- To assess viral shedding in the vaccine groups in a subset. (amended: 12-FEB-2001)

Note: the immunogenicity/stool subset is described in section 6.4. (amended: 12-FEB-2001)

For the subset of subjects who receive three doses of HRV or placebo (N~200):

- To assess serum IgA to rotavirus, two months after dose 2 and dose 3 of study vaccine or placebo.
- To assess viral shedding in the vaccine groups after the third HRV vaccine dose.
- To explore the effect of SB Biologicals' rotavirus vaccine on the immune response to concurrently administered routine vaccinations two months after the third dose of routine vaccines.

Safety/Reactogenicity

- To assess the safety and reactogenicity of two doses of SB Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given

concomitantly with routine vaccinations compared with placebo. (amended: 12-FEB-2001)

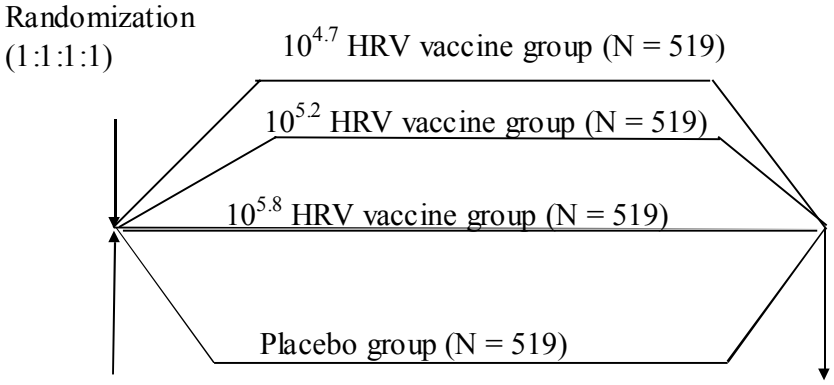
- To assess the safety and reactogenicity of the third dose of SB Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo in a subset of subjects (N~200). (amended: 3-MAY-2002)

Refer to Glossary of Terms for definition of term used

3. Study Design Overview

(amended: 12-FEB-2001) (amended: 3-MAY-2002) (amended: 20-SEP-2002) **(amended: 21 August 2003)**

For the subset of subjects who receive two doses of HRV or placebo:

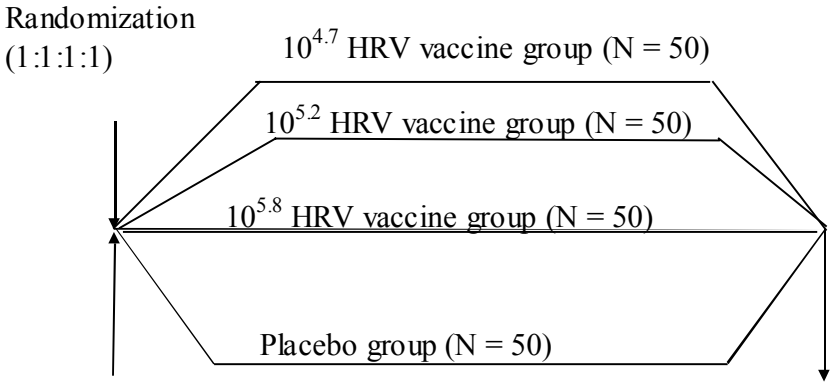


Visit 1 2 Months of Age Dose 1	Visit 2 4 Months of Age Dose 2	Visit 3 6 Months of Age Follow-up, Dose 3 of routine vaccines Interim analysis	Study visit 1 Year of Age Efficacy Follow-up/ Final Analysis	***Study visit¶*** ***2 Years of Age*** ***Efficacy*** ***Follow-up/*** ***Annex Analysis***

¶In a subset of subjects

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

For the subset of subjects who receive three doses of HRV or placebo:



Visit 1 2 Months of Age Dose 1	Visit 2 4 Months of Age Dose 2	Visit 3 6 Months of Age Dose 3*	Visit 4 8 Months of Age Follow-up	Study visit 1 Year of Age Efficacy Follow-up/ Final Analysis	***Study visit¶*** ***2 Years of Age*** ***Efficacy Follow-up/ Annex Analysis***

*HRV vaccine/placebo and routine vaccines
¶In a subset of subjects

- Experimental design: Double-blind, randomized, placebo-controlled, with four parallel groups.
  - Group A: HRV ($10^{4.7}$ ffu) vaccine.
  - Group B: HRV ($10^{5.2}$ ffu) vaccine.
  - Group C: HRV ($10^{5.8}$ ffu) vaccine. (amended: 12-FEB-2001)
  - Group D: Placebo.
- Indication: Two oral doses will be administered to healthy infants who are 2 months of age at the time of dose 1.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

- All subjects will be followed for efficacy until one year of age and a subset, about 1000 subjects, will be followed for efficacy until ***a maximum of*** two years of age. (amended: 20-SEP-2002) **(amended: 21 August 2003)**
- Blinding: double-blind for HRV vaccine and placebo. The parents/guardians of the subjects and the study personnel will be blinded to the treatment administered. Blinding will be maintained for the whole study period. Refer to section 6.5. (amended: 3-MAY-2002)
- Control: Placebo.
- Study will be conducted independently in Brazil, Mexico and Venezuela. In each country the local responsibility for directing, monitoring and supporting the study will belong to the local SB units medical staff.
- For the subjects who participate only in the first year of efficacy follow-up (until age 12 months), the intended duration of the study, per subject, will be approximately 10 months for subjects. For the subset of subjects who participate in ***the*** second efficacy follow-up ***period*** (until ***maximum*** age 24 months), the intended duration of the study, per subject, will be 22 months ***at most***. (amended: 20-SEP-2002) (Amended: 26 March 2003) **(amended: 21 August 2003)**

Study Procedures

- Hepatitis B, BCG and OPV vaccination at birth is allowed according to local Expanded Program of Immunization (EPI) [should be documented in the electronic Case Report Form (eCRF)].
- Routine vaccinations (DTPw-HB+Hib vaccine) should be administered concomitantly with the study vaccines at 2 and 4 months of age; thereafter, DTPw-HB+Hib vaccine will be given at 6 months of age. Oral polio vaccination will be given at the discretion of the investigator, but should not be administered during the period starting 2 weeks before each dose of study vaccine and ending 2 weeks after. Routine vaccinations, including OPV, must be documented in the eCRF.
- There will be no restrictions on feeding the infants before or after study vaccines' administration.
- Study visits:

Visit 1 (2 Months of Age) – Pre-vaccination blood sample from all subjects, Dose 1 of study vaccine or placebo and Dose 1 of routine vaccinations (i.e. DTPw-HB+Hib).

Visit 2 (4 Months of Age) – Blood sample in a subset (800 subjects), Dose 2 of study vaccine or placebo and Dose 2 of routine vaccinations (DTPw-HB+Hib vaccine). (amended: 12-FEB-2001)

Visit 3 (6 Months of Age) – Blood sample in a subset (800 subjects) and Dose 3 of routine vaccinations (DTPw-HB+Hib vaccine). (amended: 12-FEB-2001).

Study visit at the end of the first year of efficacy follow-up (1 Year of Age) – Blood sample from subjects who receive two doses of study vaccine or placebo, and Efficacy Follow-up. This will be the final study visit for the subjects who participate only in the first year of efficacy follow-up. (amended: 3-MAY-2002) (amended: 20-SEP-2002)

A subset of subjects (N ~ 200) enrolled in Brazil will receive a third dose of the HRV vaccine or placebo along with blood sampling at Visit 3. A study visit (Visit 4) will take place for these subjects two months after the third dose of study vaccine or placebo to collect a blood sample. For these subjects the first year of efficacy follow-up study visit will take place at approximately one year of age: a blood sample will not be taken from this subset at this visit. (amended: 3-MAY-2002) (amended: 20-SEP-2002) (amended: 26 March 2003)

Study visit at the end of the second efficacy follow-up ***period*** (approximately 18 – 24 months of age) – Efficacy Follow-up. This will be the final study visit for the subjects who participate in a second efficacy follow-up ***period.*** (amended: 3-MAY-2002) (amended: 20-SEP-2002) (amended: 26 March 2003) **(amended: 21 August 2003)**

- Active follow-up for safety and gastroenteritis via weekly visit to a subject by study personnel (Health Worker) starting 1 week after dose 1 and ending at the study visit at the end of the second efficacy follow-up period. For the subjects who participate only in the first year of efficacy follow-up, active follow-up for safety and gastroenteritis via weekly visit to a subject by study personnel (Health Worker) will end at the study visit at the end of the first efficacy follow-up period. (amended: 3-MAY-2002) (amended: 20-SEP-2002)

- 15-day follow-up period (day 0 to day 14) on solicited symptoms (fever, fussiness / irritability, diarrhea, vomiting, loss of appetite and cough/runny nose) after any dose of study vaccine using diary cards (in a subset of approximately 200 subjects after dose 3). (amended: 3-MAY-2002)
- Blood samples will be drawn from all subjects at study Visits 1, from subjects receiving two doses of study vaccine or placebo at the end of the first efficacy follow-up period and in a subset (N = 800) at Visits 2 and 3. Blood samples will be drawn from the subset receiving three doses of study vaccine or placebo (N ~ 200) at Visit 3 (two months after dose 2) and Visit 4 (two months after dose 3). (amended: 3-MAY-2002) (amended: 20-SEP-2002)
- Stool samples will be collected from a subset of 400 subjects enrolled on the day of administration of dose 1 and dose 2 and on day 7 following each dose of study vaccine (amended: 12-FEB-2001). Stool samples will be collected from the subset receiving three doses of study vaccine/placebo (N ~ 200) on the day of administration of dose 3 and on day 7 following dose 3 of study vaccine. (amended: 3-MAY-2002)
- Recording of unsolicited symptoms within 42 days after dose 1, dose 2 (in all subjects), and dose 3 (in a subset of approximately 200 subjects) of the study vaccines. (amended: 3-MAY-2002)
- Recording of serious adverse events throughout the study period.
- Data collection will be by remote data entry.
- Recruitment time will be discussed in the recruitment plan, which is summarised in Appendix C.
- Information on feedings on the day of each study vaccine administration will be recorded for all subjects. The parent/guardian will be questioned whether the child is fed with breast milk or infant formula and whether the child was fed within 60 minutes before vaccination and/or within 30 minutes after vaccination.
- For each suspected gastroenteritis episode occurring from day of dose 1 until study end, a stool sample will be collected as soon as possible after the onset of gastroenteritis and will be brought as soon as possible to the study site. A

second stool specimen will be collected if the first stool sample was not sufficient. (amended: 12-FEB-2001)

- All stool samples collected during gastroenteritis episodes will be refrigerated upon receipt by Study Personnel. A portion of the sample will be tested by Rota Ag ELISA to determine the presence of rotavirus. All positive samples will be tested by PCR to determine G type. If any G1 rotavirus is detected in the stool specimens between Visit 1 and Visit 3 (Visit 4 for the subset receiving three doses of study vaccine or placebo), vaccine virus will be differentiated from the wild type serotype by sequence analysis or an equivalent approach. In addition, rotavirus positive stool samples will be cultured locally to determine the presence/absence of mixed infections. (amended: 3-MAY-2002)
- As part of a site-specific sub-study in Venezuela, stool samples, up to a maximum of 10 over the study period, will be collected from a subset of 200 subjects enrolled in Venezuela. Also, two additional stool samples will be collected from this subset during each gastroenteritis episode occurring during the study period. (amended: 10-OCT-2001)

4. Study Cohort

4.1 Number of subjects / centers

Target enrollment was planned at 2640 (660 subjects in each group) to obtain 2360 evaluable subjects (590 each group) for the analysis of the primary objective.

However, the target sample could not be reached because of difficulty in enrolling eligible subjects for participation in the study. The final enrollment is 2276 eligible subjects. (amended: 3-MAY-2002)

This will be a multicenter study to be conducted in Brazil, Mexico and Venezuela.

Only subjects for whom the investigator believes the requirements of the protocol will be complied with should be enrolled in the study.

See Section 10.4 for a description of the criteria used in the justification of the sample size.

See Appendix C for details of the recruitment plan.

4.2 Inclusion criteria

- A male or female child between, and including 6 and 12 weeks (42-90 days) of age at the time of the first vaccination.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Written informed consent obtained from the parents or guardians of the subject.
- Born after a gestation period (between 36 and 42 weeks) or a birth weight > 2000g.

4.3 Exclusion criteria

The following criteria should be checked at the time of study entry. If any apply at the time of study entry, the subject must not be included in the study:

- Use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the study vaccine or placebo or planned use during the study period.
- Planned administration of a vaccine (including routine pediatric vaccines) not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.
- Planned administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth. (Topical steroids are allowed.)
- History of diphtheria, tetanus, pertussis, Hib disease and/ or hepatitis B.
- Previous vaccination against diphtheria, tetanus, pertussis, and/or *Haemophilus influenzae* type b.

- Use of antibiotics within 7 days preceding dose 1 (Warrants deferral of vaccination pending recovery of the subject).
- Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the GI tract or other serious medical condition as determined by the investigator.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
- History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.
- Acute disease at time of enrollment. (Acute disease is defined as the presence of moderate or severe illness with or without fever i.e. temperature ≥ 37.5°C as measured by an axillary thermometer or ≥ 38.0°C as measured by a rectal thermometer). A temperature greater than or equal to these cut-off warrants deferral of the vaccination pending recovery of the subject. (amended: 12-FEB-2001)
- Gastroenteritis within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).
- Household contact with an immunosuppressed individual or pregnant women.
- Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
- Previous confirmed occurrence of rotavirus gastroenteritis.

4.4 Elimination criteria during the study up to Visit 3 *(*up to Visit 4 for the subset of 200 subjects receiving three doses of study vaccine/placebo)

The following criteria should be checked at visits 2 and 3. These elimination criteria should be also checked on the day of dose 3 of study vaccine/placebo in the subset of subjects who receive the third dose (at Visit 4). (amended: 3-MAY-2002) If any become applicable during the study, the subject will not be required to discontinue the study but may be eliminated from the according-to-protocol analysis. See Section 10.3 for definition of study cohorts/datasets to be evaluated.

- Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.

- Use of antibiotics during the period starting from 7 days before dose 1 and 2 and ending 7 days after.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
- Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of vaccine(s) and ending 14 days after.
- Administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
- Administration of immunoglobulins and/or any blood products during the study period.
- Confirmed immunosuppressive or immunodeficient condition, including HIV.

4.5 Elimination criteria during the study from Visit 3 (from Visit 4 for the subset of 200 subjects receiving three doses of study vaccine/placebo) until the study end (amended: 3-MAY-2002) (amended: 20-SEP-2002)

The following criteria should be checked at the follow-up visit at the end of the first efficacy follow-up period and at the end of the second efficacy follow-up period as applicable. (amended: 3-MAY-2002) (amended: 20-SEP-2002)

If any become applicable during the study, the subject may be eliminated from the according-to-protocol analysis. See Section 10.3 for definition of study cohorts/datasets to be evaluated.

- Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
- Administration of immunoglobulins and/or any blood products during the study period.

- Confirmed immunosuppressive or immunodeficient condition, including HIV.

4.6 Contraindications to vaccination

SB Biologicals' HRV vaccine or placebo:

The following adverse events constitute absolute contraindications to further administration of human rotavirus vaccine or placebo; if any of these adverse events occur during the study, the subject must not receive additional doses of vaccine or placebo but may continue other study procedures at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event (see section 8.4):

- Hypersensitivity reaction due to the vaccine.
- Intussusception.

The following adverse events constitute contraindications to administration of human rotavirus vaccine or placebo at a given point in time; if any one of these adverse events occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see section 5.3) or withdrawn at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event (see section 8.4).

- Axillary/rectal temperature ≥37.5°C/38.0°C
- Gastroenteritis within 7 days preceding the study vaccine administration.

DTPw-HB+Hib vaccine:

The following adverse events constitute absolute contraindications or precautions to further administration of DTPw-HB+Hib vaccine; if any of these adverse events occurs during the study, the subject must be withdrawn and must be followed until resolution of the event, as with any adverse event (see Section 8.4):

Absolute contraindications:

- Known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B or Hib vaccines.
- Encephalopathy (not due to another identifiable cause). This is defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, and/or generalized or focal seizures that persist more than a few hours, with failure to recover within 24 hours. Even though causation by DTP-containing vaccine cannot be established, no subsequent doses of pertussis vaccine should be given.

Precautions:

If the following adverse events occur in temporal relation to DTPw-HB+Hib vaccine administration, the decision to administer additional doses of DTPw-HB+Hib vaccine should be carefully considered:

- Fever ≥ 40.5°C/≥ 40.0°C (rectal/axillary temperature) within 48 hours of vaccination not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting >3 hours, occurring within 48 hours of vaccination.
- Seizures with or without fever occurring within 3 days of vaccination.

5. Conduct of Study

5.1 Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice, the Declaration of Helsinki (Protocol Appendix A), and local rules and regulations of the country.

5.1.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The IRB/IEC must be constituted according to the local laws/customs of each participating country. It is recommended that it should include:

- At least five members.
- At least one member whose primary area of interest is in a non-scientific area.
- At least one member who is independent of the institution/ study site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the study should vote/ provide opinion on a study-related matter.

A list of IRB/IEC members and their qualifications should be obtained by the investigator.

This protocol and any other documents that the IRB/IEC may need to fulfil its responsibilities, including subject recruitment procedures, and information about payments and compensation available to subjects, will be submitted to an appropriate Committee or Board by the investigator or designate, and their written unconditional approval should be in the possession of the investigator and the sponsor before commencement of the study. Relevant SmithKline Beecham Biologicals data will be supplied by the SmithKline Beecham study monitor via the investigator (or designate) to the hospital/ university/ independent IRB/IEC for the protocol's review and approval. Verification of IRB/IEC unconditional approval of the protocol and the written informed consent statement will be transmitted by the investigator (or designate) using the standard notification form, generally prior to shipment of vaccine supplies and eCRFs to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and state the date of review.

No deviations from, or changes to, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g.,

change of monitor(s), telephone number(s)). Modifications are submitted to the IRB/IEC for information only. However, written verification that the modification was submitted should be obtained. Approvals/ verifications must be transmitted in writing to SmithKline Beecham Study Monitor.

The IRB/IEC must be informed by the investigator (or designate) of

- all subsequent protocol amendments/modifications, informed consent changes or revisions of other documents originally submitted for review
- serious and/or unexpected adverse events occurring during the study, where required
- all subsequent protocol modifications (for information)
- new information that may affect adversely the safety of the subjects or the conduct of the study
- an annual update and/or request for re-approval, where required
- when the study has been completed, where required.

5.1.2 Informed consent

The principles of informed consent in the current edition of the Declaration of Helsinki (Protocol Appendix A) should be implemented in each clinical study before any protocol-specified procedures or interventions are carried out. Informed consent will be obtained in accordance with 21 CFR 50.25.

Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC.

The written consent document will embody the elements of informed consent as described in the current edition of the Declaration of Helsinki, will adhere to the ICH Harmonized Tripartite Guideline for Good Clinical Practice and will also comply with local regulations.

An investigator or designate will describe the protocol to potential parents/guardians face to face. The Subject Information and Consent Form may

be read to the parents/guardians, but, in any event, the investigator shall give the subjects and/or parents/guardians ample opportunity to inquire about details of the study and ask any questions before dating and signing the Consent Form. All illiterate individuals will have the study, the Subject Information and Consent Form explained to them point by point by the interviewer in the presence of an impartial witness. The witness should personally sign and personally date the consent form.

Parents/guardians must be informed that the trial involves research, purpose of the trial, those aspects of the trial that are experimental, expected benefits, possible risks (including a statement that the particular treatment or procedure may involve risks to the subject which are currently unforeseeable), the expected duration of the subject's participation in the trial, the subject's responsibilities, the approximate number of subjects involved in the trial, procedures of the research study including all invasive procedures and the probability for random assignment to treatment groups. Parents/guardians be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. They must also be informed of alternative procedures that may be available and the important potential benefits and risks of these available alternative procedures. Parents/guardians must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. Parents/guardians must be informed of the anticipated financial expenses, if any, to the subject for participating in the trial as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They must be informed whom to contact (e.g. the investigator) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. Parents/guardians must be informed that the subject's participation is voluntary and that they are free to withdraw from the study for any reason at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to

participate in the trial. The extent of the confidentiality of subject records must be defined, and parents/guardians must be informed that applicable data protection legislation will be complied with. Subjects and/or parents/guardians must be informed that the monitor(s), auditor(s), IRB/IEC, and the regulatory authority (ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject and/or parent/guardian is authorizing such access. Parents/guardians must be informed that records identifying the subject will be kept confidential, and to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the subject's identity will remain confidential.

The consent form generated by the investigator with the assistance of SmithKline Beecham Biologicals, must be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC and be acceptable to SmithKline Beecham Biologicals. Consent forms must be in a language fully comprehensible to the prospective parents/guardians. Informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subject and/or parent/guardian, and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or SmithKline Beecham professional and Regulatory Compliance persons. The parent/guardian should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects and/or parents/guardians, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to parents/guardians. Oral witnessed consent will replace written consent only in countries where the local custom is contrary or if the subject's incapacity precludes this and provided that the local legal obligations are fulfilled.

5.2 General study aspects

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Each study site will receive a "Road book" providing guidelines for the conduct of the study. (amended: 12-FEB-2001)

Routine vaccinations (DTPw-HB+Hib vaccine) should be administered concomitantly with the study vaccines at 2 and 4 months of age; thereafter, DTPw-HB+Hib vaccine will be given at 6 months of age. In a subset of approximately 200 subjects the third dose of DTPw-HB/Hib will be given concomitantly with the third dose of study vaccine/placebo (amended: 3-MAY-2002). Oral polio vaccination will be given at the discretion of the investigator, but should not be administered during the period starting 2 weeks before each dose of study vaccine and ending 2 weeks after.

No restrictions on feeding the infants before or after study vaccines' administration.

The parents/guardians will be instructed to contact the investigator and his staff immediately should the subject manifest any signs or symptoms they perceive as serious. The investigator and his staff will be aware of the possible increased risk of intussusception and will consider this diagnosis among children presenting symptoms of intussusception. Symptoms consistent with intussusception are severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41°C. The investigator and his staff will take appropriate actions to evaluate and treat the condition.

Surveillance of gastroenteritis and collection of stool samples

An active surveillance for gastroenteritis will be conducted via weekly visits to a subject by study personnel (Health Worker) starting 1 week after dose 1 and ending at the final study visit (amended: 3-MAY-2002). For the subjects who participate only in the first year of efficacy follow-up, the follow-up visit at the end of the first efficacy follow-up period (at 1 year of age) will be the final visit. For the subjects who participate in ~~a~~ ***the*** second efficacy follow-up ***period***, the follow-up visit at the end of the second efficacy follow-up period (at ***maximum*** 24 months of age) will be the final visit. **(amended: 21 August 2003)** There need

be no weekly follow-up in weeks when a study clinic visit is scheduled. The weekly follow-up by a Health Worker may be done at the subject's home, at a health clinic, or other mutually convenient place. At weekly follow-up, Health Workers will inquire about the occurrence of gastroenteritis and serious adverse events (disabling illness, hospitalization, death). In cases of gastroenteritis, parents should contact the study site personnel. Health Workers will collect a stool specimen (if required) and ensure the diary card is being completed properly; they will collect completed diary cards when the gastroenteritis has ended. Health Workers will ensure parents properly complete diary cards recording solicited symptoms for 15 days (days 0-14) and unsolicited symptoms/medication within 42 days after each dose of study vaccine; they will collect these diary cards. (amended: 12-FEB-2001) (amended: 20-SEP-2002)

Two occurrences of gastroenteritis should be classified as separate episodes if there are 5 or more symptom-free days between the episodes.

Parents/guardians should use the containers to collect stool samples. If this is not possible, soiled diapers should be individually placed in the ziplock bags and sealed. The parents/guardians/health worker should write the date of collection on the container/ziplock bag label with a black ink or ballpoint pen. (amended: 12-FEB-2001)

5.3 Outline of study procedures

Subjects who receive two doses of study vaccine will have four study visits. Subjects who receive three doses of study vaccine will have five study visits.

All subjects who have not completed the follow-up visit at 1 year of age as of October 31, 2002, will have an additional follow-up visit at approximately 24 months of age. The number of subjects in this case is expected to be about 1000. (amended: 20-SEP-2002)

The study procedures at each visit are outlined below. (amended: 3-MAY-2002) (amended: 20-SEP-2002)

Age	**2 months**	**4 months**	**6 months**	**8 months**	**1 year**	**18-24 Mo**
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4 DOSE 3 SUBSET ONLY***	**END OF 1ST EFFICACY PERIOD**	**END OF 2ND EFFICACY PERIOD**
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 MO 4**	**Post vacc 3 MO 6**	**Post vacc 2 MO 10**	
Informed consent	•					
Medical history	•					
Check of inclusion criteria	•					
Check of exclusion criteria	•					
Check of elimination criteria		•	•	•	•	•
Check of contraindications	•	•	•			
Physical examination	•	•	•	•	•	•
Pre-vaccination body temperature	•	•	•			
Measure/record height and weight	•	•	•	•	•	•
Blood sampling	• (1 ml of blood)	• (1 ml of blood in a subset#)	• (3 mls of blood in a subset#) • (1 ml of blood in dose 3 subset*)	• (3 mls of blood in dose 3 subset*)	• (3 mls of blood in a subset#, 1 ml for subjects receiving two doses)	
Randomisation	•					
Stool samples will be collected from a subset (N = 400) on the day of administration of dose 1 and dose 2 and on day 7 following each dose. Stool samples will be collected from a subset (N ~ 200) on the day of administration of dose 3 and on day 7 following dose 3	•	•	•			
Study Vaccine	•	•	• (dose 3 subset*)			
Routine Vaccination	•	•	•			
Daily post-vaccination recording of solicited symptoms (days 0–14) by parents/guardians	•	•	• (dose 3 subset*)			
Collection of stool samples if the child is suspected to have gastroenteritis	•	•	•	•	•	•

Age	**2 months**	**4 months**	**6 months**	**8 months**	**1 year**	**18-24 Mo**
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4 DOSE 3 SUBSET ONLY***	**END OF 1ST EFFICACY PERIOD**	**END OF 2ND EFFICACY PERIOD**
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 MO 4**	**Post vacc 3 MO 6**	**Post vacc 2 MO 10**	
Recording of solicited symptoms, non serious adverse events within 42 days after dose 1, dose 2 and dose 3 (in a subset), by investigator		•	•	• (dose 3 subset*)		
Contact (field visit) every week	◊	◊	◊	◊	◊	◊
Return of GE diary	•	•	•	• (dose 3 subset*)	•	•
GE diary transcription		•	•	• (dose 3 subset*)	•	•
Documentation of routine EPI vaccines	•	•	•	• (dose 3 subset*)	•	•
Recording medication	•	•	•	• (dose 3 subset*)		
Reporting of Serious Adverse Events occurring throughout the study period	•	•	•	• dose 3 (subset*)	•	•
Study Conclusion					•¶	•§

#Subset for immunogenicity evaluation (N = 800) (amended: 26 March 2003)
*Subset receiving three doses of study vaccine/placebo (N = 200)
◊ is used to indicate a study procedure which does not require documentation in the individual eCRFs.
¶For subjects who participate only in the first year of efficacy follow-up
§For subjects who participate in a second efficacy follow-up ***period*** **(amended: 21 August 2003)**

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed. These intervals determine a subject's evaluability in the according to protocol analyses (see Sections 4.4 and 10.3 for details of criteria for evaluability and cohorts to be analyzed).

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Intervals between study visits* for subjects receiving 2 doses of study vaccine/placebo will be as follows (amended: 3-MAY-2002) (amended: 20-SEP-2002) **(amended: 21 August 2003)**

Interval	Size of interval
1 (Visit 1→Visit 2)	49 - 83 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→ First efficacy follow-up visit)	160 - 200 days
4 (First efficacy follow-up visit → Second efficacy follow-up visit)	***Brazil and Venezuela: until 01 -> 31 October 2003*** Mexico: June 1 -> 30, 2003 (after the end of rotavirus season)

*The date of the previous visit is the reference date. (amended: 26 March 2003)

Intervals between study visits* for subjects included in the subset receiving 3 doses of study vaccine/placebo will be as follows (amended: 3-MAY-2002) **(amended: 21 August 2003)**

Interval	Size of interval
1 (Visit 1→Visit 2)	49 - 83 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→Visit 4)	49 – 83 days
4 (Visit 3→ First efficacy follow-up visit)	160 - 200 days
5 (First efficacy follow-up visit → Second efficacy follow-up visit)	***Brazil and Venezuela: until 01 -> 31 October 2003*** Mexico: June 1 -> 30, 2003 (after the end of rotavirus season)

*The date of the previous visit is the reference date. (amended: 26 March 2003)

5.4 Detailed description of study stages/visits

Visit 1: Dose 1	**6 to 12 weeks (42 to 90 days) of age**

- Written informed consent signed by the parents/guardians of the subject.
- Medical history taking.
- Physical examination with measurement and recording of height and weight. For logistical convenience, any physical examination data recorded up to one week before vaccination may be used.
- Check of inclusion/exclusion criteria.
- Check of contraindications to vaccination.
- Recording of previous/concomitant medication (see section 6.9).
- Pre-vaccination assessment of axillary or rectal body temperature (Fever ≥ 37.5°C axillary or 38.0°C rectally warrants deferral of vaccination).
- Collection of blood sample from all subjects for serology: a minimum of 1 ml of whole blood to provide a minimum of 0.4 ml of serum according to instructions in Appendix D. (For logistical convenience, any blood sample taken in conditions appropriate to the study protocol in terms of volume, serum separation and storage conditions within a period of maximum one week prior to administration of the first dose may be used as a pre-vaccination blood sample provided an informed consent has been signed by the parent/guardian of the subject prior to the procedure).

  When materials are provided by SB Biologicals, it is mandatory that all clinical samples (including serum samples) be collected using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from analysis. The investigator must ensure that his/her personnel and the laboratory (ies) under his/her supervision comply with this requirement.

- Randomisation (or subject) number attribution. (amended: 12-FEB-2001)

- Collection of a stool sample at the day of or 1 day prior to vaccination from a subset of 400 subjects enrolled, to determine the presence of rotavirus. (amended: 12-FEB-2001)
- Recording the subject's feeding schedule. The parent/guardian will be questioned whether the child is fed with breast milk or infant formula and whether the child was fed within 60 minutes before vaccination and/or 30 minutes after vaccination.
- Administration of study vaccines:
  - Oral administration of first dose of the study vaccine or placebo according to the guidelines set out in Section 6.2. Study vaccine must be given before the routine vaccines. If regurgitation occurs immediately (within 30 minutes) after administration, do not give another dose and record in the eCRF.
- Administration of routine vaccines: DTPw-HB+Hib vaccine recorded in eCRF).
- The vaccinees will be observed closely for at least **30** minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.
- At the end of the 30 minutes of observation period, a diary card will be provided to the parents/guardians of the subjects to record body temperature (measured by a axillary or rectal route), the number of looser than normal stools passed by the subject, the number of vomiting episodes, any loss of appetite, any fussiness/irritability, any cough/runny nose during the 15-day solicited follow-up period, as well as unsolicited symptoms occurring within 42 days after dose 1.
- The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

Interval between Visit 1 and 2

Day 0 to Day 14 (At bedtime):

- The following data will be recorded on the diary-card: (amended: 12-FEB-2001)

- general solicited symptoms (fever, irritability/fussiness, diarrhea, vomiting, loss of appetite, cough/runny nose)
- unsolicited symptoms, including any SAE

Day 7 ± 1:

- Collection of a stool sample in a subset (400 subjects). (amended: 12-FEB-2001)

Any time between Visit 1 and Visit 2

- Recording of unsolicited symptoms, including any SAE. (amended: 12-FEB-2001)
- A Health Worker will visit the parent/guardian weekly (except for weeks when a study clinic visit is scheduled) to assess the completion or collection of diary card information, check on the occurrence of any adverse event, including any SAE or gastroenteritis episodes and if appropriate, collect stool samples.
- Parents/guardians of all subjects will be instructed to collect one stool sample if they suspect that the subject has gastroenteritis symptoms (diarrhea) between Visits 1 and 2. A second stool sample will be collected on a different day if the first stool sample was insufficient. Two occurrences of gastroenteritis symptoms should be classified as separate episodes if there are 5 or more symptom-free days between the episodes. The study personnel may organise transportation of the stool samples.
- Diary cards will also be provided to the parents/guardians of all subjects to daily record the following information until symptoms resolve during each suspected episode of gastroenteritis occurring between visits: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. Rehydration or other medication will be recorded. (amended: 12-FEB-2001)

Visit 2: Vaccine dose 2	**4 Months of Age (49 to 83 days after 1st vaccination)**

- Physical examination with measurement and recording of height and weight.
- Check elimination criteria.

- Check contraindications.
- Recording previous/concomitant medication (see section 6.9).
- Pre-vaccination assessment of axillary or rectal body temperature (Fever ≥ 37.5°C axillary or 38.0°C rectally warrants deferral of vaccination).
- Collection of blood sample in a subset (800 subjects) for serology: a minimum of 1 ml of whole blood to provide a minimum of 0.4 ml of serum according to instructions in Appendix D. (amended: 12-FEB-2001)
- Collection of a stool sample at the day of or 1 day prior to vaccination from a subset (400 subjects) to determine the presence of rotavirus. (amended: 12-FEB-2001)
- Collection and verification of diary card containing information on adverse experiences occurring from Visit 1 until Visit 2. The investigator will verify the diary card and transcribe the information into the appropriate sections of the eCRF, in English. The study monitor may help in this translation. Any unreturned diary cards will be sought through telephone call(s) or any other convenient procedure.
- Recording of unsolicited adverse events that may have occurred on day 0-42 post-vaccination.
- Recording of serious adverse events that may have occurred since previous visit.
- Recording the subject's feeding schedule. The parent/guardian will be questioned whether the child is fed with breast milk or infant formula and whether the child was fed within 60 minutes before vaccination and/or 30 minutes after vaccination.
- Administration of study vaccines:
  - Oral administration of second dose of the study vaccine or placebo according to the guidelines set out in Section 6.2. Study vaccine must be given before the routine vaccines. If regurgitation occurs immediately (within 30 minutes) after administration, do not give another dose and record in the eCRF.
- Administration of routine vaccines: DTPw-HB+Hib vaccine recorded in eCRF).

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

- The vaccinees will be observed closely for at least **30** minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.
- At the end of the 30 minutes of observation period, a diary card will be provided to the parents/guardians of the subjects to record body temperature (measured by a axillary/rectal route), the number of looser than normal stools passed by the subject, the number of vomiting episodes, any loss of appetite, any fussiness/irritability, any cough/runny nose during the 15-day solicited follow-up period, as well as unsolicited symptoms occurring within 42 days after dose 2.
- The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

Interval between Visit 2 and 3

Day 0 to Day 14 (At bedtime):

- The following data will be recorded on the diary card: (amended: 12-FEB-2001)
  - general solicited symptoms (fever, irritability/fussiness, diarrhea, vomiting, loss of appetite, cough/runny nose)
  - unsolicited symptoms, including any SAE

Day 7 ± 1:

- Collection of a stool sample in a subset (400 subjects). (amended: 12-FEB-2001)

Any time between Visit 2 and Visit 3

- Recording of unsolicited symptoms, including any SAE. (amended: 12-FEB-2001)
- A Health Worker will visit the parent/guardian weekly (except for weeks when a study clinic visit is scheduled) to assess the completion or collection of diary card information, check on the occurrence of any adverse event,

including any SAE or gastroenteritis episodes and if appropriate, collect stool samples.

- Parents/guardians of all subjects will be instructed to collect one stool sample if they suspect that the subject has gastroenteritis symptoms (diarrhea) between Visits 2 and 3. A second stool sample will be collected on a different day if the first stool sample was insufficient. Two occurrences of gastroenteritis symptoms should be classified as separate episodes if there are 5 or more symptom-free days between the episodes. The study personnel may organise transportation of the stool samples.
- Diary cards will also be provided to the parents/guardians of all subjects to daily record the following information until symptoms resolve during each suspected episode of gastroenteritis occurring between visits: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. Rehydration or other medication will be recorded. (amended: 12-FEB-2001)

Visit 3: Dose 3 of routine vaccines and Follow-up	**6 Months of Age (49 to 83 days after 2nd vaccination)**

- Physical examination with measurement and recording of height and weight.
- Check elimination criteria.
- Check contraindications.
- Recording previous/concomitant medication (see section 6.9).
- Pre-vaccination assessment of axillary or rectal body temperature (Fever ≥ 37.5°C axillary or 38.0°C rectally warrants deferral of vaccination).
- Collection of blood sample in a subset (800 subjects) for serology: a minimum of 3 mls of whole blood to provide a minimum of 1.5 mls of serum according to instructions in Appendix D. (amended: 12-FEB-2001)
- Collection and verification of diary card containing information on adverse experiences occurring from Visit 2 until Visit 3. The investigator will verify the diary card(s) and transcribe the information into the appropriate sections of the eCRF, in English. The study monitor may help in this translation. Any

unreturned diary cards will be sought through telephone call(s) or any other convenient procedure.

- Recording of unsolicited adverse events that may have occurred on day 0-42 after dose 2.
- Recording of serious adverse events that may have occurred since previous visit.
- Administration of routine vaccines: DTPw-HB+Hib vaccine (recorded in eCRF).
- The vaccinees will be observed closely for at least **15** minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.
- The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

In addition, to the above mentioned study procedure, the following study procedures will be done at Visit 3 for the subset of approximately 200 subjects enrolled in Brazil and Venezuela who receive three doses of study vaccine or placebo: (amended: 3-MAY-2002)

- Collection of blood sample for serology: a minimum of 1 mls of whole blood to provide a minimum of 0.5 mls of serum according to instructions in Appendix D.
- Collection of a stool sample at the day of or 1 day prior to vaccination.
- Administration of study vaccines:
  - Oral administration of third dose of the study vaccine or placebo according to the guidelines set out in Section 6.2. Study vaccine must be given before the routine vaccines. If regurgitation occurs immediately (within 30 minutes) after administration, do not give another dose and record in the eCRF.
- The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.

- At the end of the 30 minutes of observation period, a diary card will be provided to the parents/guardians of the subjects who received the third dose of study vaccine/placebo to record body temperature (measured by a axillary/rectal route), the number of looser than normal stools passed by the subject, the number of vomiting episodes, any loss of appetite, any fussiness/irritability, any cough/runny nose during the 15-day solicited follow-up period, as well as unsolicited symptoms occurring within 42 days after dose 3.
- Recording the subject's feeding schedule for the subset who received the third dose of study vaccine/placebo. The parent/guardian will be questioned whether the child is fed with breast milk or infant formula and whether the child was fed within 60 minutes before vaccination and/or 30 minutes after vaccination.

NOTE: Subjects receiving 3 doses of study vaccine or placebo will have Visit 4 approximately two months after Visit 3. These subjects will be followed until 2 years of age maximum (all of them), thus the final visit will be at end of second efficacy follow-up (maximum 24 months of age). (amended: 20-SEP-2002) **(amended: 21 August 2003)**

Interval between Visit 3 and 4 for subjects included in the subset receiving 3 doses of study vaccine/placebo (amended: 3-MAY-2002)

Day 7 +/-1: collection of a stool sample

Day 0 to Day 14 (At bedtime):

- The following data will be recorded on the diary card:
  - general solicited symptoms (fever, irritability/fussiness, diarrhea, vomiting, loss of appetite, cough/runny nose)
  - unsolicited symptoms, including any SAE

Interval between Visit 3 and end of the first efficacy follow-up period (amended: 3-MAY-2002) (amended: 20-SEP-2002)

Continued efficacy follow-up:

- A Health Worker will visit the parent/guardian weekly (except for weeks when a study clinic visit is scheduled) to assess the completion or collection of diary card information, check on the occurrence of SAE or gastroenteritis episodes and if appropriate, collect stool samples. (amended: 12-FEB-2001)
- Parents/guardians of all subjects will be instructed to collect one stool sample if they suspect that the subject has gastroenteritis symptoms (diarrhea) between Visits 3 and the final study visit. A second stool sample will be collected on a different day if the first stool sample was insufficient. Two occurrences of gastroenteritis symptoms should be classified as separate episodes if there are 5 or more symptom-free days between the episodes. The study personnel may organise transportation of the stool samples.
- Diary cards will also be provided to the parents/guardians of all subjects to daily record the following information until symptoms resolve during each suspected episode of gastroenteritis occurring between visits: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. Rehydration or other medication will be recorded. (amended: 12-FEB-2001)

Visit 4 only for subjects receiving 3 doses of study vaccine/placebo: Follow-up (amended: 3-MAY-2002)	**8 Months of Age (49 to 83 days after Visit 3)**

- Physical examination with measurement and recording of height and weight.
- Check elimination criteria.
- Recording previous/concomitant medication (see section 6.9).
- Collection of blood sample for serology: a minimum of 3 mls of whole blood to provide a minimum of 1.5 mls of serum according to instructions in Appendix D.
- Collection and verification of diary card containing information on adverse experiences occurring from Visit 3 until Visit 4. The investigator will verify the diary card(s) and transcribe the information into the appropriate sections of the eCRF, in English. The study monitor may help in this translation. Any

unreturned diary cards will be sought through telephone call(s) or any other convenient procedure.

- Recording of unsolicited adverse events that may have occurred on day 0-42 after dose 3.
- Recording of serious adverse events that may have occurred since previous visit.
- The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

First efficacy follow-up visit (Visit 4 for subjects receiving 2 doses of study vaccine/placebo or Visit 5 for subjects receiving 3 doses of study vaccine/placebo): Efficacy Follow-up (amended: 3-MAY-2002) (amended: 20-SEP-2002)	**1 Year of Age (160 – 200 days after Visit 3)**

- Physical examination with measurement and recording of height and weight.
- Check elimination criteria.
- Collection of blood sample from subjects for serology: a minimum of 3 mls of whole blood for the subjects in the subset (800 subjects) and a minimum of 1 ml in subjects who received two doses of study vaccine or placebo. (amended: 12-FEB-2001) (amended: 3-MAY-2002)
- Recording of diary card information on gastroenteritis episodes which occurred since the previous visit. The investigator will transcribe the information into the appropriate sections of the eCRF. (amended: 3-MAY-2002)
- Recording of serious adverse events that may have occurred since previous visit.
- Document the administration of routine EPI vaccines since the previous visit. (amended: 12-FEB-2001) (amended: 3-MAY-2002) (amended: 20-SEP-2002)
- Study Conclusion for the subjects who participate only in the first year of efficacy follow-up. (amended: 20-SEP-2002)

Interval between end of the first efficacy follow-up period and end of the second efficacy follow-up period (amended: 20-SEP-2002)

Continued efficacy follow-up:

- A Health Worker will visit the parent/guardian weekly (except for weeks when a study clinic visit is scheduled) to assess the completion or collection of diary card information, check on the occurrence of SAE or gastroenteritis episodes and if appropriate, collect stool samples.
- Parents/guardians of all subjects will be instructed to collect one stool sample if they suspect that the subject has gastroenteritis symptoms (diarrhea). A second stool sample will be collected on a different day if the first stool sample was insufficient. Two occurrences of gastroenteritis symptoms should be classified as separate episodes if there are 5 or more symptom-free days between the episodes. The study personnel may organise transportation of the stool samples.
- Diary cards will also be provided to the parents/guardians of all subjects to daily record the following information until symptoms resolve during each suspected episode of gastroenteritis occurring between visits: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. Rehydration or other medication will be recorded.

(amended: 20-SEP-2002) (amended: 26 March 2003) **(amended: 21 August 2003)**

Second efficacy follow-up visit: Efficacy Follow-up	***Maximum*** 24 months of age (Brazil and Venezuela: ***until 01 -> 31 October 2003***) (Mexico: June 1 -> 30, 2003 after the end of RV season)

- Physical examination with measurement and recording of height and weight.
- Check elimination criteria.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

- Recording of diary card information on gastroenteritis episodes which occurred since the previous visit. The investigator will transcribe the information into the appropriate sections of the eCRF.
- Recording of serious adverse events that may have occurred since previous visit.
- Document the administration of routine EPI vaccines since the previous visit.
- Study Conclusion for the subjects who participate in the second efficacy follow-up ***period***.

Please refer to Appendix L for information on additional stool sampling for the subset of 200 subjects participating in the site-specific study in Venezuela. (amended: 10-OCT-2001)

5.5 Sample handling and analysis

5.5.1 Treatment and storage of biological samples

See Appendix D of the protocol for details of treatment and storage of biological samples.

See Appendix E for instructions for shipment of biological samples.

See Appendix I for intussusception related specimens.

5.5.2 Laboratory assays

See Appendix F for details.

Stool Analysis

Stool samples will be collected from a subset of 400 subjects enrolled, on the day of or 1 day prior to administration of dose 1 and dose 2 and on day 7 following each dose. Stool samples will be also collected from the subset receiving three doses of study vaccine/placebo (N ~ 200) on the day of or 1 day prior to

administration of dose 3 and on day 7 following dose 3 of study vaccine. (amended: 3-MAY-2002).

Any detection of the vaccine virus in any stool collected after vaccination up to Visit 3 (Visit 4 for subset receiving three doses of study vaccine/placebo) will be taken as evidence of a vaccine response (i.e. vaccine take), as long as the subject had a negative ELISA test for RV Ag on day 0. Additionally, any detection of Rota-Ag in a stool collected 7 (± 1) days after vaccination will be regarded as evidence of a vaccine take if the pre-vaccination stool sample collected 1 week earlier had a negative test for Rota-Ag. Also, stool samples will be collected during each episode of gastroenteritis which occur from the first dose until study end. During the first year of efficacy follow-up, if rotavirus is detected (by rapid rotavirus detection kit) in the stool sample, part of the stool sample should be analysed locally for culture of enteric pathogens such as Salmonella, Shigella, and Campylobacter. During the second efficacy follow-up ***period***, the stool samples will be tested only for rotavirus, there will be no local testing for the presence of enteric pathogens. ETEC and EPEC will be determined at a central laboratory. The other part of the stool sample will be sent to core laboratory(ies) to be tested by ELISA to confirm the presence of rotavirus. Diagnosis of rotavirus gastroenteritis will be by ELISA. If positive, the sample will be tested by PCR to determine G type. If any G1 rotavirus is detected in the stool specimens between Visit 1 to Visit 3 (Visit 4 for the subset receiving three doses of study vaccine or placebo), vaccine virus will be differentiated from the wild type serotype by sequence analysis or an equivalent approach. (amended: 12-FEB-2001) (amended: 20-SEP-2002). (amended: 26 March 2003) **(amended: 21 August 2003)**

Please refer to Appendix L for information on laboratory assays to be performed on additional stool samples collected from the subset of 200 subjects participating in the site-specific study in Venezuela. (amended: 10-OCT-2001)

Any additional testing on stools will be performed if deemed necessary by SmithKline Beecham Biologicals if any findings in the present study or in other studies necessitate investigation of the immunogenicity of the vaccine. (amended: 12-FEB-2001)

Immunogenicity (amended: 3-MAY-2002) (amended: 20-SEP-2002)

For all subjects, a minimum of 1 ml of whole blood will be collected at Visit 1. For subjects receiving two doses of HRV vaccine or placebo, for the immunogenicity subset (N=800), a minimum of 1 ml of whole blood will be collected at Visit 2 and a minimum of 3 mls of whole blood will be collected at Visit 3 and at the end of the first efficacy follow-up period, using tubes with serum separator. For all other subjects receiving two doses of vaccine, a minimum of 1 ml of whole blood will be collected at the final study visit. For the subset receiving three doses of study vaccine/placebo (N ~ 200), a minimum of 1 ml of whole blood will be collected at Visit 3 and a minimum of 3 mls of whole blood will be collected at two months after dose 3 (Visit 4). After blood centrifugation and serum separation, samples will be stored at –20°C until collection by the sponsor. The aliquots of serum (approximately 0.4/1.5 ml) will be sent to core laboratory(ies) for the following tests:

1. Anti-rotavirus IgA antibodies by ELISA. The current cut-off is 20 U/ml, based on the technical assay by Ward [7,8] and adapted by SB Biologicals.
2. Antibodies to the Hib polysaccharide PRP will be measured by ELISA technique.
3. IgG antibodies against pertussis components will be measured by ELISA techniques [12, 13, 14].
4. Anti-diphtheria and anti-tetanus antibody concentrations will be measured by ELISA and expressed in international units per ml (IU/ml), with respect to a reference serum. It is generally accepted that for both diphtheria and tetanus, antibody concentrations ≥ 0.01 IU/ml, as measured by in vivo neutralization tests, are protective. It has been previously demonstrated that a good correlation exists between in vivo neutralization tests and the ELISAs for antibodies to diphtheria and tetanus toxoids but this correlation may be reduced at antibody concentrations <0.1 IU/ml. For this reason, a antibody concentration of 0.1 IU/ml by ELISA (corresponding to approximately 3 times the lower quantitation limit of the assays) will be arbitrarily and conservatively set as the cut-off (for both anti-diphtheria and anti-tetanus ELISAs) [15, 16].

5. Antibodies to the HbsAg will be measured by ELISA technique.
6. Antibodies against polio virus types 1, 2 and 3 will be determined by a virus micro-neutralization test adapted from the World Health Organization Guidelines for WHO/EPI Collaborative Studies on Poliomyelitis – Standard Procedure for Determining Immunity to Poliovirus using the Microneutralization Test (WHO/EPI/GEN 93.9). The lowest dilution at which serum samples will be tested is 1:8, from which a test will be considered positive. Titers will be expressed in terms of the 50 % inhibitory dose (ID50). [17].

Antigen	**Assay method**	**Test Kit/ Manufacturer**	**Assay unit**	**Assay cut-off**	**Core Laboratory**
rotavirus	IgA ELISA	in-house	U/ml	20	TBD
anti-PRP	ELISA	in-house	mcg/ml	0.15	TBD (amended: 12-FEB-2001)
anti-D	ELISA	in-house	IU/ml	0.1	TBD
anti-T	ELISA	in-house	IU/ml	0.1	TBD
anti-BPT	ELISA	in-house	EL.U/ml	15	TBD
anti-HBs	ELISA	in-house	mcg/ml	10	TBD
anti-polio 1	micro-neutralization test	in-house	-	8	TBD
anti-polio 2	micro-neutralization test	in-house	-	8	TBD
anti-polio 3	micro-neutralization test	in-house	-	8	TBD

TBD = To be determined

5.5.3 Serology plan

(amended: 20-SEP-2002) (amended: 26 March 2003)

Study Group	Blood sampling timepoint			Antigen	No. subjects
	Timing	**Month**	**Visit no.**		
A, B, C & D	Pre	0	1	rotavirus only	2276
A, B, C & D	Post I	2	2	rotavirus only	800
A, B, C & D	Post II MO 4	4	3	all rotavirus only	800 200*
A, B, C & D	Post III MO 6	6	4	all	200*
A, B, C & D	Post II MO 10	10	End of 1st efficacy period visit	concomitant rotavirus	800 2155#

* =subset of subjects who receive 3 doses of the study vaccine or placebo
# = only subjects who receive 2 doses of the study vaccine or placebo
(amended: 12-FEB-2001) (amended: 3-MAY-2002)

In case of insufficient serum sample volume to perform assays for all antibodies, antibodies will be evaluated according to the following priority ranking:

1. ELISA concentrations to rotavirus
2. anti-PRP
3. anti-HBs
4. anti-diphtheria
5. anti-tetanus
6. anti-BPT
7. anti-poliovirus type 1; anti-poliovirus type 2; anti-poliovirus type 3

Any additional serology on antigens contained in the study vaccines or routine vaccines will be performed if deemed necessary by SmithKline Beecham Biologicals if any findings in the present study or in other studies necessitate

investigation of the immunogenicity of the vaccine. In this case, the ranking above may also be changed.

6. Study Vaccine(s) and Administration

6.1 Study vaccine(s)

All candidate Human rotavirus vaccines to be used have been developed and manufactured by SmithKline Beecham Biologicals.

The Quality Control Standards and Requirements for each candidate vaccine are described in separate release protocols and the required approvals have been obtained. Commercial vaccines (DTPw-HB+Hib vaccine) are assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

6.1.1 SmithKline Beecham Biologicals' HRV vaccine

The HRV vaccine manufactured by SmithKline Beecham Biologicals is a whitish to slightly pink colored freeze-dried cake or powder supplied in vials to be reconstituted with the diluent supplied separately.

Each vial contains the following components:

Active ingredient:

89-12 HRV strain (RIX4414)	$10^{4.7}$, $10^{5.2}$ or $10^{5.8}$ ffu (amended: 12-FEB-2001)

Excipients (stabilizers):

Dulbecco's Modified Eagle Medium (DMEM)	3.7 mg
Sucrose	9 mg
Dextran	18 mg
Sorbitol	13.5 mg
Amino acids	9 mg

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

One lot of each viral concentration will be used.

Refer to Appendix G for details of vaccine supplies.

6.1.2 Placebo

The placebo manufactured by SmithKline Beecham Biologicals is a whitish to slightly pink colored freeze-dried cake or powder supplied in vials to be reconstituted with the diluent supplied separately.

Each vial contains the following components:

Excipients (stabilizers):

Dulbecco's Modified Eagle Medium (DMEM)	3.7 mg
Sucrose	9 mg
Dextran	18 mg
Sorbitol	13.5 mg
Amino acids	9 mg

Two lots will be used. (amended: 3-MAY-2002)

Refer to Appendix G for details of vaccine supplies.

6.1.3 SmithKline Beecham Biologicals' $CaCO_3$ buffer

The $CaCO_3$ buffer manufactured by SmithKline Beecham Biologicals is a suspension supplied in pre-filled syringes.

Each pre-filled syringe contains the following components:

$CaCO_3$	60 mg
Xanthane 0.25 % in water for injection	1.0 ml

6.1.4 Commercial EPI vaccines

Vaccine	Lot no.	Formulation One dose (0.5ml) of vaccine contains	Presentation
DTPw-HB+Hib vaccine	Commercial Lots will be used (amended: 12-FEB-2001)	Each 0.5 mL dose contains: Whole cell pertussis ≥ 4 IU Diphtheria toxoid ≥ 30 IU (25 Lf); Tetanus toxoid ≥ 60 IU (10 Lf); HBsAg 10 mcg; PRP 10 mcg bound to 30 mcg tetanus toxoid; 2-phenoxyethanol, polysorbate 20, Sodium chloride, thiomersal, lactose, water for injection	DTPw-HB+Hib vaccine is presented as 2 individual components. DTPw-HB vaccine and Hib vaccine. (amended: 12-FEB-2001)
Polio Sabin	Commercial Lots will be used (amended: 12-FEB-2001)	Poliovirus type 1 (LS-c, 2ab) 10^6 $TCID_{50}$; Poliovirus type 2 (P712, Ch, 2ab) 10^5 $TCID_{50}$; Poliovirus type 3 (Leon $12a_1b$) $10^{5.5}$ $TCID_{50}$; Magnesium chloride; Neomycin	Liquid (amended: 12-FEB-2001)

6.2 Dosage and administration

(amended: 3-MAY-2002)

Visit	Vaccination	Dose	Vaccine	Route[1]	Site[2]	Side
1, 2	Rotavirus	1	Human Rotavirus	Oral	NA	NA
3 (Subset)	Rotavirus	1	Human Rotavirus	Oral	NA	NA
1, 2,3	DTPw, HB, Hib	1	DTPw-HB+Hib	IM	T	Investigator discretion
	OPV*	1	*Polio Sabin*	Oral	NA	NA

1 Intramuscular (IM)
2 Anterolateral thigh (T)
* Oral polio vaccination will be given at the discretion of the investigator, but should not be administered during the period starting 2 weeks before each dose of study vaccine and ending 2 weeks after.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

To prepare the vaccine or placebo for administration, the entire content (1.0 ml) of one pre-filled syringe containing the $CaCO_3$ buffer should be injected into the vial of the lyophilized product (vaccine or placebo). The vial should be shaken well to resuspend the vaccine. The entire volume of the resuspended product should be withdrawn into the same syringe, the needle should be discarded and the resuspended product should then be administered promptly as a single oral dose. If the blinded vaccines can not be used promptly, they can be stored in the refrigerator for up to 24 hours.

The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.

Injection technique

In order to ensure proper intramuscular injection of the non-HRV vaccines, a 23- or 25- gauge needle long enough to reach the substance of the muscle should be used (1 inch long). The following injection technique is recommended [21].

The needle should be inserted in the upper lateral quadrant of the thigh, directly inferiorly at an angle of 45 degrees with the long axis of the leg, with the subject supine. During the injection, the tissues of the injection site are compressed with the free hand, increasing the penetrable muscle mass and stabilizing the extremity.

DTPw-HB+Hib vaccine

The vaccine will be prepared and administered according to the recommendations made by the manufacturer. DTPw-HB+Hib is prepared by reconstitution of the Hib pellet with the DTPw-HB suspension. Withdraw 0.5 ml of the vaccine from the vial and administer DTPw-HB+Hib vaccine intramuscularly into the anterolateral thigh.

Polio Sabin

The vaccine will be prepared and administered according to the recommendations made by the manufacturer. Oral polio vaccination will be given at the discretion

of the investigator, but should not be administered during the period starting 2 weeks before each dose of study vaccine and ending 2 weeks after.

6.3 Storage

All vaccines and placebo vials, as well as the diluent must be stored in a safe and locked place with no access for unauthorized personnel. They must be kept in the refrigerator (+2°C to +8°C) and must not be frozen. Storage temperature should be monitored at least once per week. It is advisable to have a back-up refrigerator in case of power failure/ breakdown.

6.4 Treatment allocation and randomisation

The target sample size was planned at 2640 enrolled subjects to reach 2360 subjects evaluable for efficacy analysis, with the following distribution (amended: 3-MAY-2002):

HRV ($10^{4.7}$ ffu) group:	660 subjects
HRV ($10^{5.2}$ ffu) group:	660 subjects
HRV ($10^{5.8}$ ffu) group:	660 subjects (amended: 12-FEB-2001)
Control group (placebo):	660 subjects

Randomisation of supplies

A randomisation list will be generated at SmithKline Beecham Biologicals, Rixensart, using a standard SAS program and will be used to number the vaccines. A blocking scheme randomisation (1:1:1:1 ratio) will be used to ensure that balance between treatments is maintained: a randomisation number will identify uniquely the vaccine doses to be administered to the same subject.

To allow SmithKline Beecham to take advantage of greater rates of recruitment than anticipated at individual centres in this multicentre study, and to thus reduce the overall study recruitment period, a 10% over-randomisation of supplies will be prepared. However, the enrolment will be terminated when 2640 subjects have been enrolled. The enrolment in Mexico will be terminated by end December

2001 to avoid vaccinating subjects during the rotavirus season. Thus, no further subjects will be enrolled in Mexico after December 31, 2001. Enrolment of eligible subjects will continue in Venezuela and Brazil to compensate the lower recruitment in Mexico. The vaccine doses will be distributed to the study centre while respecting the randomisation block size. (amended: 12-FEB-2001) (amended: 11-DEC-2001)

Randomisation of subjects

The randomisation will be performed using a central randomisation system on Internet. The randomisation algorithm uses a minimisation procedure stratified by centre [23]. All countries/centers must use internet randomization, however in case of unexpected technical problems, the classical randomization will be done. (amended: 12-FEB-2001)

For centres using the Internet randomisation, when a subject is eligible and the parent/guardian has given informed consent, the person who is in charge of the vaccination will access the randomisation system on Internet. Upon providing the subject initials and birth date, the randomisation system will determine the vaccine number to be used for the subject. For centres using the classical randomisation, subjects will be administered the vaccine dose with the lowest number still available at the study centre. The vaccine number will also be used as patient identification number (PID) for all data collected on the subject under the study. (amended: 12-FEB-2001)

Subset Definitions (amended: 20-SEP-2002)

The first 200 (100) subjects enrolled in each country will provide a blood (stool) sample. The remaining subset of 200 (100) blood (stool) samples will come indifferently from any of the participating countries, according to the order of enrollment. In all, the subset that provides additional blood samples will contain approximately 800 subjects and the subset that provides stool samples on day 0 and day 7 will contain approximately 400 subjects. (amended: 12-FEB-2001). (amended: 26 March 2003)

A subset of approximately 200 subjects among the last enrolled in Brazil will constitute the subset that will receive three doses of study vaccine/placebo. (amended: 3-MAY-2002). The sub-group that receives 3 doses is constituted of about 121 subjects (and not 200 as mentioned above) as the protocol was not approved in Venezuela. As outlined in the study procedures, these subjects also provide stool samples. (amended: 26 March 2003)

All subjects who have not completed the follow-up visit at 1 year of age as of October 31, 2002, will have an extended follow-up for rotavirus gastroenteritis with an additional follow-up visit at approximately 18 - 24 months of age. The number of subjects in this case is expected to be of approximately 1000. (amended: 20-SEP-2002) (amended: 26 March 2003) **(amended: 21 August 2003)**

6.5 Method of blinding and breaking the study blind

The study will be performed under double-blind conditions – the parents/guardians of the subjects and the study personnel will be unaware of the administered treatment (HRV vaccine and placebo).

Selected persons using the central randomisation system can perform unblinding. The code can be broken by the Clinical Safety physician only in the case of medical events, which the investigator/physician in charge of the subject feels, cannot be treated without knowing the identity of the study vaccine.

The Data Safety Monitoring Board (DSMB) will have access to the unblinding and may at its discretion identify the product administered to any subject to evaluate whether enrollment in the study should be halted.

In the event that the code is broken, the reason must be recorded in the eCRF and in the subject's medical record.

6.6 Replacement of unusable vaccine doses

Additional doses will be provided to replace those that are unusable (see Appendix G for details of supplies). (See RDE booklet for details of internet randomisation)

In addition to the vials numbered from 1 up to the planned number of subjects, an additional 5% of study vaccines and routine vaccines will be supplied for replacement in case of breakage or bad storage conditions. For HRV/placebo, the identification of the replacement vial will be obtained from the central study system to ensure that a vaccine identical to the subjects' vaccine is administered. Although the sponsor need not be notified immediately in these cases, documentation of the use of the replacement vial for study vaccines and reason for using it must be recorded by the investigator on the vaccine administration page of the eCRF and on the vaccine accountability form.

6.7 Packaging

See Appendix G.

6.8 Vaccine accountability

See Appendix G.

6.9 Concomitant medication/treatment

Only at visit 1, 2, 3 (for all subjects) and at visit 4 (for the subset receiving three doses of study vaccine/placebo), the investigator should question the subject or their legal representative about any medication taken. (amended: 3-MAY-2002)

Any immunosuppressants or other immune-modifying drugs or treatments administered at ANY time during the period starting 30 days prior to the first dose of study vaccine(s) and ending at Visit 3 (Visit 4 for the subset of subjects receiving a third dose of study vaccine/placebo) must be recorded in the eCRF with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment. Any vaccine other than the study vaccine(s) administered at ANY time during the period

starting at birth and ending at the last study visit must be recorded in the eCRF. Any antibiotics administered within 7 days preceding each study vaccine/placebo administration and during the first 7 days after each study vaccine/placebo administration and any antipyretics administered at ANY time during the period starting 30 days prior to the first dose of study vaccine(s) and ending one month (minimum 30 days) after the last dose of study vaccine/placebo must be recorded in the eCRF with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment. (amended: 3-MAY-2002)

Any other concomitant medication administered prophylactically in anticipation of reaction to study vaccination must also be recorded in the eCRF with trade name and/or generic name of the medication, total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'

7. Health Economics

Not applicable.

8. Adverse Events

The recording of adverse events is an important aspect of study documentation. It is the responsibility of the investigator to document all adverse events according to the detailed guidelines set out below.

The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

8.1 Eliciting and documenting adverse events

Adverse event definition

An adverse event includes any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs,

symptoms and/or laboratory detected changes occurring in any phase of the clinical study whether associated with the study vaccine, active comparator or placebo and whether or not considered vaccination related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, or vaccine or drug interaction. Anticipated day-to-day fluctuations of pre-existing conditions, that do not represent a clinically significant exacerbation need not be considered adverse events. Discrete episodes of chronic conditions occurring during a study period should be reported as adverse events in order to assess changes in frequency or severity.

Adverse events should be documented in terms of a medical diagnosis(es). When this is not possible, the adverse event should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject at each study visit.

Pre-existing conditions or signs and/or symptoms (including any which are not recognized at study entry but are recognized during the study period) present in a subject prior to the start of the study should be recorded on the Medical History form within the subject's eCRF.

Adverse events which occur after informed consent is obtained, but prior to vaccination, will be documented in the Medical History form within the subject's eCRF as instructed by the SmithKline Beecham Study Monitor.

Although not considered as an adverse event, hospitalization for either elective surgery related to a pre-existing condition which did not increase in severity or frequency following initiation of the study, or for routine clinical procedures (including hospitalization for “social” reasons) that are not the result of an adverse event, must be recorded in the eCRF. If the hospitalization arises from a pre-existing condition, or was planned prior to the first vaccination, it should be recorded in the Medical History form of the eCRF. If it was planned after the first vaccination, it should be recorded in the adverse event page of the eCRF. In both cases, it should be recorded as ‘Hospitalization (Not an adverse event)’, and the relationship to vaccination will be checked “No”.

N.B. Adverse events to be recorded as endpoints are described in Section 8.1.1. All other adverse events will be recorded as unsolicited adverse events.

Surveillance period for occurrence of adverse events

All non-serious adverse events occurring within 42 days after each study vaccine/placebo dose must be recorded on the Adverse Event form in the subject's eCRF, irrespective of severity or whether or not they are considered vaccination-related. (amended: 3-MAY-2002)

Additionally, all serious adverse events (see Section 8.5) occurring during the period starting from the day of administration of the first dose of study vaccine(s) to each subject and ending up to the study end must be recorded. See Section 8.5.2 for instructions for reporting and recording of serious adverse events.

Instances of death, cancer or congenital abnormality in offspring if brought to the attention of the investigator AT ANY TIME after cessation of study AND suspected by the investigator to be related to study vaccine, should be reported to the Study Contact for Reporting Serious Adverse Events (see Section 8.5.2).

Recording adverse events

At each visit/assessment, all adverse events either observed by the investigator or one of his clinical collaborators or reported by the parents/guardians spontaneously or in response to a direct question will be evaluated by the investigator. Adverse events not previously documented in the study will be recorded in the Adverse Event form within the subject's eCRF. The nature of each event, date and time (where appropriate) of onset, outcome, intensity and relationship to vaccination should be established. Details of any corrective treatment should be recorded on the appropriate page of the eCRF. See Section 8.5 for instructions for reporting and recording of serious adverse events.

The parents/guardians will be instructed to contact the investigator and his staff immediately should the subject manifest any signs or symptoms they perceive as serious. The investigator and his staff will be aware of the possible increased risk

of intussusception and will consider this diagnosis among children presenting these symptoms. Symptoms consistent with intussusception are severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41°C. The investigator and his staff will take appropriate actions to treat the condition.

In case a subject is diagnosed with intussusception immediate reporting to the sponsor will be mandatory. Refer to section 8.5. The diagnosis of intussusception should be documented by radiography. See Appendix I for instruction on the evaluation of intussusception. (amended: 12-FEB-2001)

Each case of suspected or confirmed intussusception will be reviewed by the DSMB.

As a consistent method of soliciting adverse events, the subject or their legal representative should be asked a non-leading question such as:

"Has your child acted differently or felt different in any way since receiving the vaccine or since the last visit?"

N.B. The investigator should record only those adverse events having occurred within the time frames defined above.

Adverse events already documented in the eCRF, i.e. at a previous assessment, and designated as 'ongoing' should be reviewed at subsequent visits, as necessary. If these have resolved, the documentation in the eCRF should be completed. N.B. If an adverse event changes in frequency or intensity during a study period, a new record of the event will be started.

8.1.1 Solicited adverse events

General adverse events

A 15-day follow-up period (day 0 to day 14) of solicited adverse experiences will be performed by the parents/guardians after each study vaccine dose. Data

concerning the following general adverse experiences will be solicited using diary cards provided by the sponsor.

- Fever
- Fussiness/Irritability
- Diarrhea
- Vomiting
- Loss of appetite
- Cough/runny nose

N.B. Axillary/rectal temperature will be recorded in the evening. Should temperature measurement additionally be performed at another time of day, the highest temperature will be recorded.

8.1.2 Surveillance of gastroenteritis

Gastroenteritis is defined as diarrhea. Refer to the Glossary of Terms for definition of diarrhea.

Subjects enrolled in this study will be followed from the day of first vaccination until study end for the occurrence of gastroenteritis. For each episode of gastroenteritis, the parent/guardian will be instructed to daily record the following on a diary card until symptoms resolve: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject and to record any medication, including oral rehydration therapy. (amended: 20-SEP-2002) (amended: 26 March 2003)

For each gastroenteritis episode, the parents/guardians of all subjects will be instructed to collect one stool sample within 7 days of onset. A second stool sample will be collected on a different day if the first stool sample was insufficient. Two occurrences of gastroenteritis symptoms should be classified as separate episodes if there are 5 or more symptom-free days between the episodes.

8.2 Assessment of intensity

Two scoring systems will be used to assess the intensity of fever, diarrhea and vomiting - one for assessment of these symptoms occurring during the 15-day solicited follow-up period (scoring system for solicited AEs) and the second for assessment of these symptoms during a gastroenteritis episode (scoring system for efficacy).

It is justified to use two different scoring systems for the assessment of these symptoms to allow appropriate evaluation of two different outcomes (reactogenicity and efficacy).

The scoring system for fever, diarrhea and vomiting as solicited AEs is similar to the scoring system used in the studies with the candidate HRV vaccine that have been already initiated. The use of the same scoring system for solicited AEs across studies will provide consistent information on the reactogenicity of the vaccine.

The scoring system for fever, diarrhea and vomiting occurring during a gastroenteritis episode is similar to the 20-point scoring system proposed by Ruuska and Vesikari [1]. This 20-point scoring system presents the full clinical picture of gastroenteritis in a balanced manner. Additionally, this 20-point scoring was shown to give the best distinction in the mean clinical severity of rotavirus and non-rotavirus diarrhea.

8.2.1 Solicited symptoms

Intensity of the following solicited general symptoms occurring during the solicited 15-day follow-up period should be assessed as follows:

Adverse Event	Intensity grade	Parameter
Fever*		Record axillary/rectal temperature in °C
Fussiness/Irritability	0	Behavior as usual
	1	Crying more than usual/ no effect on normal activity

	2	Crying more than usual/ interferes with normal activity
	3	Crying that cannot be comforted/ prevents normal activity
Diarrhea¶		Record the number of looser than normal stools/day
Vomiting§		Record the number of vomiting episodes/day
Loss of appetite	0	Normal
	1	Eating less than usual/ no effect on normal activity
	2	Eating less than usual/ interferes with normal activity
	3	Not eating at all
Cough/runny nose	0	Normal
	1	Cough/runny nose which is easily tolerated
	2	Cough/runny nose which interferes with daily activity
	3	Cough/runny nose which prevents daily activity

*Fever is defined as rectal temperature ≥38°C / axillary temperature ≥ 37.5°C.

¶Diarrhea is defined as 3 or more looser than normal stools within a day.

§Vomiting is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

The maximum intensity of fever recorded during the 15-day follow-up period will be scored at SmithKline Beecham Biologicals as follows:

Grade	Rectal	Axillary
0	< 38.0°C	< 37.5°C
1	38.0°C to 38.5°C	37.5°C to 38.0°C
2	38.6°C to 39.5°C	38.1°C to 39.0°C
3	>39.5°C	>39.0°C

The maximum intensity of diarrhea and vomiting occurring during the solicited 15-day follow-up period will be scored at SmithKline Beecham Biologicals as follows:

Adverse Event	Intensity grade	Parameter
Diarrhea	0	Normal (0-2 looser than normal stools/day)
	1	3 looser than normal stools/day
	2	4-5 looser than normal stools/day
	3	≥6 looser than normal stools/day
Vomiting	0	Normal (no emesis)
	1	1 episode of vomiting/day
	2	2 episodes of vomiting/day
	3	≥ 3 episodes of vomiting/day

8.2.2 Unsolicited symptoms

The maximum intensity of all other adverse events, except symptoms of gastroenteritis, should be assigned to one of the following categories:

0 = No adverse event
1 = An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 = An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3 = An adverse event which prevents normal, everyday activities. (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten/ a day-care center and would cause the parents/ guardians to seek medical advice.)

8.2.3 Intensity of gastroenteritis episodes for efficacy analysis

A 20-point scale will be used to assess the severity of each gastroenteritis episode [1]. In this system, points will be assigned at SmithKline Beecham Biologicals according to duration and intensity of diarrhea and vomiting, the intensity of

fever, presence of dehydration or hospitalization for each episode of gastroenteritis as shown below:

Adverse Experience		**Points**
Duration of looser than normal stools (days)		
1-4		1
5		2
≥ 6		3
Maximum number of looser than normal stools /24 hours		
1-3		1
4-5		2
≥ 6		3
Duration of vomiting (days)		
1		1
2		2
≥ 3		3
Maximum number of episodes of vomiting/24 hours		
1		1
2-4		2
≥ 5		3
Fever*		
Rectally	**Axillary**	
37.1 – 38.4°C	36.6 – 37.9°C	1
38.5 – 38.9°C	38.0 – 38.4°C	2
≥ 39°C	≥ 38.5°C	3
Dehydration**		
1-5%		2
≥ 6%		3
Treatment		
Rehydration		1
Hospitalization+		2

* The highest temperature recorded during the episode will be scored.
** Dehydration will be assessed clinically based on World Health Organization criteria.
+ Includes a detention (> 6 hours) in a treatment facility for rehydration under observation.

A score ≥11 is prospectively defined as severe.
A score <7 is prospectively defined as mild.
A score 7 - 10 is prospectively defined as moderate.

8.3 Assessment of causality

Every effort should be made by the investigator to explain each adverse event and assess its causal relationship, if any, to administration of the study vaccine(s).

In case of concomitant administration of multiple vaccines, it will not be possible to determine causal relationship of general adverse events to the individual vaccines administered. The investigator should, therefore, assess whether the adverse event could be causally related to study vaccination rather than to the individual vaccines.

The degree of certainty with which an adverse event can be attributed to administration of the study vaccine(s) (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of one or more of the following:

- Reaction of similar nature having previously been observed with this type of vaccine and/or formulation.
- The event having often been reported in literature for similar types of vaccines.
- The event being temporally associated with vaccination or reproduced on re-vaccination.

Causality should be assessed by the investigator using the following method:

In your opinion, did the vaccine(s) possibly contribute to the adverse event?

NO : The adverse event is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the adverse event.

YES : There is a reasonable possibility that the vaccine contributed to the adverse event.

Non-serious and serious adverse events will be evaluated as two distinct events given their different medical nature. If an event meets the criteria to be determined "serious" (see Section 8.5 for definition of serious adverse event), it will be examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each serious adverse event.

Other possible contributors include:

- Medical history
- Other medication
- Protocol required procedure
- Lack of efficacy of the vaccine
- Erroneous administration
- Other cause (specify).

8.4 Following-up of adverse events and assessment of outcome

Investigators should follow-up subjects with serious adverse events (including intussusception) until the event has subsided (disappeared) or until the condition has stabilized. Investigators should follow-up subjects with non-serious adverse events until study conclusion for that subject. Reports relative to the subsequent course of an adverse event noted for any subject must be submitted to the Study Monitor.

Outcome should be assessed as:

1 = Recovered

2 = Recovered with sequelae
3 = Ongoing at subject study conclusion
4 = Died
5 = Unknown.

8.5 Serious adverse events

8.5.1 Definition of a serious adverse event

A serious adverse event is any untoward medical occurrence that results in death, is life threatening*, results in persistent or significant disability/incapacity†, requires in-patient hospitalization‡ or prolongation of existing hospitalization or is a congenital anomaly/birth defect in the offspring of a study subject. In addition, important medical events (i.e. intussusception) that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such treatments are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not results in hospitalization; or development of drug dependency or drug abuse.)

Although not considered as 'serious adverse events', cancers should be reported in the same way as serious adverse events.

*Life threatening—definition: An adverse event is life threatening if the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

†Disabling/incapacitating—definition: An adverse event is incapacitating or disabling if the event results in a substantial disruption of the subject's ability to carry out normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle).

‡Hospitalization: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for treatment that would not have been appropriate in the physician's office or out-patient setting.

Hospitalization for either elective surgery related to a pre-existing condition which did not increase in severity or frequency following initiation of the study or for routine clinical procedures¶ (including hospitalization for "social" reasons) that are not the result of an adverse event need not be considered as adverse events and are therefore not serious adverse events.

¶Routine Clinical Procedure—definition: One which is defined as a procedure which may take place during the study period and should not interfere with the study vaccine administration or any of the ongoing protocol specific procedures.

N.B. If anything untoward is reported during an elective procedure, that occurrence must be reported as an adverse event, either 'serious' or 'non-serious' according to the usual criteria.

When in doubt as to whether 'hospitalization' occurred or was necessary, the adverse event should be considered serious.

8.5.2 Reporting serious adverse events

Any serious adverse events occurring during the period starting from the day of administration of the first dose of study vaccine(s) up to the study end, whether or not considered to be related to the study vaccines, must be reported by the investigator to the SmithKline Beecham Study Contact for Serious Adverse Event Reporting by fax within 24 hours (1 calendar day) of his/her becoming aware of the event.

The investigator will document all available information regarding the serious adverse event on the Serious Adverse Event pages contained in the individual eCRF and fax to the SmithKline Beecham Contact for Serious Adverse Event Reporting. The investigator should not wait to receive additional information to

fully document the event before notifying SmithKline Beecham Biologicals of a serious adverse event. This initial notification should include, as a minimum, sufficient information to permit identification of:

- the reporter
- the subject
- study vaccine(s)
- adverse event(s)
- date of onset.

In the event of a death or a serious adverse event determined by the investigator to be related to vaccination, receipt of the fax must be confirmed by telephone call. The Standard Verbal Autopsy Questionnaire (see Annex 1) ([1]) should be completed and transmitted by the investigator (or designee), in addition to the SAE report, for all deaths during the study period irrespective of relationship to vaccination and whether a written autopsy is performed or not. The Standard Verbal Autopsy Questionnaire does not replace the written autopsy. Refer to Annex 1. (amended: 26 March 2003)

The initial fax report should be followed by a full summary utilizing the SmithKline Beecham Biologicals Serious Adverse Event pages in the individual eCRF detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be obtained.

For cases of intussusception, the investigator will document all available information on the Serious Adverse Event pages contained in the individual eCRF. In addition, the investigator will complete the Intussusception Form when all data has become available and fax it to the SmithKline Beecham Contact for Serious Adverse Event Reporting.

Instances of death, cancer or congenital abnormality in offspring if brought to the attention of the investigator AT ANY TIME after cessation of study vaccine AND suspected by the investigator to be related to study vaccine, should be reported to the Study Contact for Serious Adverse Event reporting.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

(amended: 12-FEB-2001) (modified: 14-MAY-2001) (amended: 11-DEC-2001) (amended: 3-MAY-2002)

Study Contact for Reporting Serious Adverse Events	
Brazil Medical Monitor: [redacted] MD GSK Jacarepaguá Estrada dos Bandeirantes 8464 - Jacarepaguá Rio de Janeiro - RJ Brasil CEP 22783-110 Phone: [redacted] (amended: 26 March 2003) Fax: [redacted]	Clinical Research Associate: [redacted] GlaxoSmithKline Diretoria Médica - Pesquisa Clinica - II Andar Estrada Dos Bandeirantes, 8464 Jacarepagua CEP: 22783-110 Rio de Janeiro, Brazil Tel: [redacted] Cell: [redacted] Fax: [redacted]
Mexico Medical Monitor: Dr. [redacted] Calzada Mexico Xochimilco N° 4900 1er piso Colonia San Lorenzo Huipulco Delegacion Tlalpan CP 14370, Mexico D.F Tel: 52 [redacted] Cell: [redacted] Fax: [redacted]	Clinical Research Associate: [redacted] Calzada Mexico Xochimilco N° 4900 1er piso Colonia San Lorenzo Huipulco Delegacion Tlalpan CP 14370, Mexico D.F Tel: [redacted] Cell: [redacted] Fax: [redacted]
Venezuela Medical Monitor: Dr. [redacted] SmithKline Beecham Venezuela Calle La Guarita Edf. Los Frailes. Piso 3 Chuao / Caracas Venezuela (modified: 14-MAY-2001)	Clinical Research Associate: [redacted] SmithKline Beecham, Colombia Avenida El Dorado No 91 - 50 Bogota, Colombia

Tel: [redacted] Mobile: [redacted] Fax: [redacted] (amended: 11-JULY-2002)	Tel: [redacted] Fax: [redacted] (amended: 11-JULY-2002)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Back-up Study Contact for Reporting Serious Adverse Events
Manager Clinical Safety Vaccines
[redacted]
Tel: [redacted] Fax: [redacted]
Mobile phone for 24/24 hour and 7/7 day availability: [redacted]

8.6 Pregnancy

Not applicable

8.7 Treatment of adverse events

Treatment of any adverse event is at the sole discretion of the investigator and according to current Good Medical Practice. The applied measures should be recorded in the eCRF of the vaccinee.

Treatment of gastroenteritis

The standard treatment will be oral rehydration followed by rapid introduction of normal full feedings according to the subject's age. The subject should be hospitalized for treatment if necessary.

9. Subject Completion and Drop-out

9.1 Definition

From an analysis perspective, any subject who does not come back for the final study visit is a drop-out for the efficacy analysis. A subject who returns for the final study visit is considered to have completed the study. (amended: 3-MAY-2002)

9.2 Procedures for handling drop-outs

Investigators should make an attempt to contact those subjects who do not return for scheduled visits or follow-up. Information gathered should be described on the Study Conclusion page of the eCRF and on Medication/Adverse event forms.

9.3 Reasons for drop-out

It should be specified on the Study Conclusion page of the eCRF, which of the following possible reasons were responsible for drop-out of the subject from the study:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (specify)
- Consent withdrawal, not due to an adverse event
- Migrated/moved from the study area
- Lost to follow-up
- Other (specify).

10. Data Evaluation: criteria for evaluation of objectives

10.1 Primary endpoint

For the subset of subjects who receive two doses of HRV or placebo (N=2076). (amended: 3-MAY-2002)

- Occurrence of any rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period.

10.2 Secondary endpoints

(amended: 3-MAY-2002) (amended: 20-SEP-2002)

Efficacy endpoints

For the subset of subjects who receive two doses of HRV or placebo (N=2076).

- Occurrence of severe rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
- Occurrence of rotavirus gastroenteritis due to virus types heterologous to vaccine strain during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period. (amended: 12-FEB-2001)
- Occurrence of any and severe pure rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
- Occurrence of rotavirus gastroenteritis in which there is at least one other pathogen during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
- Occurrence of hospitalization for rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.

For the subset of subjects who receive three doses of HRV or placebo (N~200):

- Occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the first efficacy follow-up period.

For the subset of subjects who participate in a second efficacy follow-up ***period*** (until ***maximum*** age 24 months): (amended: 26 March 2003) **(amended: 21 August 2003)**

- For the subset of subjects who receive two doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.
- For the subset of subjects who receive two doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the second efficacy follow-up period.
- For the subset of subjects who receive three doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period

starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.

- For the subset of subjects who receive three doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the second efficacy follow-up period.

Immunogenicity endpoints

For the subset of subjects who receive two doses of HRV or placebo (N=2076).

- Serum rotavirus IgA antibody titers at Visit 1 and the end of the first efficacy follow-up period ~~final visit~~ and at Visits 2 and 3 in a subset (N=800).
- Proportion of subjects with vaccine take at visits 2 and 3 in a subset (N=800).
- Vaccine take and GMTs of rotavirus IgA ELISA will be calculated in a subset for breast fed infants compared with formula fed infants for the following 3 categories: 1) whether the infant received no food 1 hour prior to and 30 minutes after dose 1 or dose 2 (as reported by the mother); 2) whether the infant received food 1 hour prior to dose 1 or dose 2 (as reported by the mother); and 3) whether the infant received food within 30 minutes after dose 1 or dose 2.
- Viral shedding in the vaccine groups in a subset (N = 400).

Two months after dose 2 (at Visit 3) and at year 1 in a subset (800 subjects). (amended: 12-FEB-2001)

- GMTs for anti-PRP, anti-diphtheria and anti-tetanus toxoids, anti-BPT, anti-polio type 1, 2 and 3 and anti-HBs.
- Seroprotection status:
  - ◊ anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
  - ◊ anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-HBs antibody concentrations ≥ 10.0 mcg/ml
  - ◊ anti-polio type 1 antibody titers ≥ 8
  - ◊ anti-polio type 2 antibody titers ≥ 8

  - ◊ anti-polio type 3 antibody titers ≥ 8
- Seropositivity status:
  - ◊ anti-BPT antibody concentrations ≥ 15 EL.U/ml

For the subset of subjects who receive three doses of HRV or placebo (N~200):

- Serum rotavirus IgA antibody titers at visit 1, 3 and 4.
- GMTs for anti-PRP, anti-diphtheria and anti-tetanus toxoids, anti-BPT, anti-polio types 1, 2 and 3 and anti-HBs, two months after dose 3.
- Seroprotection status two months after dose 3:
  - ◊ anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
  - ◊ anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-HBs antibody concentrations ≥ 10.0 mcg/ml
  - ◊ anti-polio type 1 antibody titers ≥ 8
  - ◊ anti-polio type 2 antibody titers ≥ 8
  - ◊ anti-polio type 3 antibody titers ≥ 8
- Seropositivity status two months after dose 3:
  - ◊ anti-BPT antibody concentrations ≥ 15 EL.U/ml
- Viral shedding in the vaccine groups on the day of and on day 7 after dose 3.

Safety endpoints

- For each type of solicited symptoms, occurrence of the symptom within the 15-day solicited follow-up period after any dose of study vaccine (in a subset after dose 3).
- Occurrence of unsolicited symptoms within 42 days after dose 1, dose 2 (in all subjects) and dose 3 (in a subset), according to WHO classification.
- Occurrence of serious adverse events throughout the entire study period.

Definitions

Diarrhea: Three or more looser than normal stools within a day.

First year of efficacy follow-up period: Each subject will be followed for the efficacy analysis starting from two weeks post dose 2 until the age of approximately one year. (amended: 20-SEP-2002)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Second efficacy follow-up period: Approximately 1000 subject will be followed for a second efficacy analysis either until ***01 -> 31 October 2003*** (for subjects from Brazil and Venezuela) or until the end of the 2003 rotavirus season (for subjects from Mexico) (amended: 26 March 2003) **(amended: 21 August 2003)**

Gastroenteritis: Diarrhea.

Two occurrences of gastroenteritis will be classified as separate episodes if there are 5 or more symptom-free days between the episodes.

Mixed rotavirus gastroenteritis: Gastroenteritis associated with rotavirus and at least one other pathogen.

Pure rotavirus gastroenteritis: Rotavirus gastroenteritis with no other concurrent pathogen infection.

Rotavirus gastroenteritis: All rotavirus gastroenteritis (pure and mixed rotavirus gastroenteritis).

Rotavirus gastroenteritis for efficacy analysis: An episode of gastroenteritis (diarrhea) occurring at least two weeks after dose 2 in which rotavirus other than vaccine strain is identified in a stool sample collected not later than 7 days after the onset of gastroenteritis symptoms.

Severe rotavirus gastroenteritis: An episode of rotavirus gastroenteritis with score greater than 11 on a 20 point scoring system.

Vaccine take: For subjects previously uninfected with rotavirus before vaccination, appearance of serum IgA to rotavirus in post-immunization sera at a titer ≥ 20 U/ml or vaccine virus shedding in any stool sample collected from Visit 1 to Visit 3.

Vomiting One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

10.3 Study cohorts/data sets to be evaluated

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Four subject cohorts will be evaluated:

Total cohort

The Total cohort will include all enrolled subjects for whom data are available. For the Total cohort analysis of safety, this will include all enrolled subjects for whom safety data are available (i.e. solicited or unsolicited data is available). For the Total cohort analysis of immunogenicity, this will include enrolled subjects for whom immunogenicity data are available.

For the Total analysis of efficacy, this will include all enrolled subjects for whom efficacy data are available.

According-to-protocol (ATP) cohort for analysis of safety

The ATP cohort for analysis of safety will include all subjects:

- who have received at least one dose of study vaccine/control according to their random assignment,
- with sufficient data to perform an analysis of safety (at least one documented dose),
- who have not received a vaccine not specified or forbidden in the protocol,
- for whom the randomisation code has not been broken.

ATP cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity will include all subjects from the ATP cohort of safety who met all eligibility criteria, complied with the procedures defined in the protocol and for whom immunogenicity data are available for rotavirus IgA antibodies at pre-vaccination timepoint and 2 months after dose 2.

For inclusion in the ATP cohort for immunogenicity, intervals between visits 1 and 2 and between visits 2 and 3 need to be at least 49 days and must not exceed 83 days. (amended: 12-FEB-2001)

ATP cohort for efficacy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

The ATP cohort for efficacy will include all subjects from the ATP cohort of safety with sufficient data to perform an analysis of efficacy (had follow-up beyond 2 weeks after dose 2, no evidence of rotavirus infection before vaccination and had received 2 doses of rotavirus/placebo vaccine). The ATP cohort for efficacy will be used to evaluate efficacy and the persistence of immune response at the end of the first efficacy follow-up period visit. (amended: 3-MAY-2002) (amended: 20-SEP-2002)

The analysis of immunogenicity on the ATP cohort will be the primary analyses. The analyses of the total cohort for immunogenicity will only be performed if more than 5% of the enrolled subjects are excluded from the corresponding ATP cohort. In such case, the total cohort analyses will evaluate whether exclusion from the ATP cohort could have biased the results.

The ATP efficacy cohort will be used for the primary analysis of efficacy. An analysis of efficacy based on the total cohort will also be performed.

The total cohort will be used for the primary analysis of safety. The analysis on the ATP cohort for safety will only be performed if more than 5% of the enrolled subjects are excluded from the ATP safety cohort.

The analyses of safety, immunogenicity and efficacy for the subset of subjects who received 3 doses of HRV or placebo will be performed on the total cohort. (amended: 3-MAY-2002)

10.4 Estimated sample size

The primary objective is to demonstrate that, for a range of viral concentration ($10^{4.7}$-ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' HRV vaccine, two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations can prevent rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the first efficacy follow-up period following vaccination. (amended: 12-FEB-2001) (amended: 20-SEP-2002)

The analysis will consist in looking at the pooled vaccine groups versus placebo and each vaccine group versus placebo. (amended: 12-FEB-2001)

In order to control the risk of falsely concluding below 5%, the primary objective will be addressed using a hierarchical testing. Pooled vaccine groups will be first tested and, only if efficacy has been demonstrated, will the vaccine with a viral concentration of $10^{5.8}$ ffu be tested. Likewise, only if efficacy of vaccine with a viral concentration of $10^{5.8}$ ffu has been demonstrated, will the vaccine with a viral concentration of $10^{5.2}$ ffu be tested. Likewise, only if efficacy of vaccine with a viral concentration of $10^{5.2}$ ffu has been demonstrated, will the vaccine with a viral concentration of $10^{4.7}$ ffu be tested. Efficacy will be established if the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the efficacy follow-up period following vaccination in the HRV group is statistically significantly lower than in the placebo group (two-sided Fisher Exact test: $p < 0.05$). (amended: 12-FEB-2001)

The target sample size was planned at 2640 enrolled subjects to reach 2360 subjects in the ATP cohort of efficacy (590 in each group). However, the target sample size has been reduced because of difficulty in enrolling eligible subjects for participation in the study. In addition, a subset of approximately 200 subjects will receive 3 doses of HRV vaccine or placebo. Target enrollment for subjects who will receive only 2 doses of HRV vaccine or placebo is estimated to be 2076 eligible subjects leaving 460 evaluable subjects per group for the analysis of the primary objective. (amended: 3-MAY-2002)

Table 10.4.1 indicates the level of accuracy that can be expected for the evaluation of efficacy for a vaccine group to any rotavirus gastroenteritis (primary objective) and to severe rotavirus gastroenteritis (secondary objective) with this sample size. Power is higher for the evaluation of efficacy on pooled vaccine groups. (amended: 12-FEB-2001)

Table 10.4-1: Power to get an exact 95% CI for the vaccine efficacy above a specific cut-off (N=460 subjects by group, power based on 1.000 simulations using Proc StatXact)[see Appendix J for mathematical details) (amended: 3-MAY-2002)

% of subjects reporting rotavirus gastroenteritis in the placebo group from two weeks after dose 2 until the end of the efficacy follow-up period following vaccination	% of subjects reporting rotavirus gastroenteritis in the vaccine group from two weeks after dose 2 until the end of the efficacy follow-up period following vaccination	Efficacy (%)	Cut-off			
			0%	10%	20%	30%
Any Gastroenteritis						
12%*	3.6%	70%	99.7%	99.2%	97%	88.9%
12%*	4.8%	60%	96.8%	92.0%	81.8%	58.1%
12%*	6 %	50%	84.1%	71.1%	48.8%	26.7%
10%	3%	70%	98.8%	97.4%	92.4%	82.2%
10%	4%	60%	93.5%	84.8%	71.4%	51.2%
10%	5%	50%	77.4%	61.7%	41.4%	20.5%
Severe Gastroenteritis						
4%*	0.8%	80%	89%	84%	76%	
4%*	1%	75%	80%	74%	63%	
4%*	1.2%	70%	72%	62%	50%	
3%	0.6%	80%	75%	68%	61%	
3%	0.75%	75%	63%	52%	44%	
3%	0.9%	70%	56%	45%	37%	

*anticipated incidence rate

With respect to the year 2 efficacy follow-up, considering an attack rate of 12% for any gastroenteritis, a 60% VE and a sample size of 200 in each vaccine group, the power to detect a statistically significant vaccine effect with the pooled

vaccine group and each vaccine group is 88% and 67% (2 sided fisher exact test, alpha=5%, no adjustment for multiplicity. (amended: 20-SEP-2002)

A secondary objective is to assess the immunogenicity of the concomitant routine vaccinations (diphtheria, tetanus, pertussis, PRP and HBs) in each group, two months after the second dose of the primary vaccination course and 6 months after the third dose.

Using an estimation of the seroprotection rates between 90% and 98% and an anti-BPT GMT of 27.3 (with a standard deviation of 0.332) (reference study: DTPw-HBV-Hib-003), and assuming that the rates / GMT are the same in the vaccine and placebo groups, a subset of 175 evaluable subjects by group will provide 80% global power that, for all vaccine groups, all the 95%CIs on the decrease in seroprotection rates with the vaccine group as compared to the placebo group are below 15% and that the 95%CIs on the fold decrease in anti-BPT GMTs with the vaccine group as compared to the placebo group is below 1.5 (power based on 1000 simulations with proc StatXact for the difference in seroprotection rates and using Nquery for the ratio of anti-BPT GMTs, one sided equivalence test, alpha=2.5%).

Allowing for up to 12% of subjects who may not be evaluable for the immunogenicity analysis, a total of 200 subjects by group will be bled.

10.5 Final analyses

The final analysis will be performed at the end of the first efficacy follow-up period, after all enrolled subjects have completed the study visit at the end of the first efficacy follow-up period. Two interim analyses will be performed on immunogenicity and reactogenicity of the vaccines to provide early information on dose selection. Two interim analyses on efficacy against any and severe rotavirus gastroenteritis will be performed to obtain early efficacy data. The interim results will be descriptive limited to summaries by group. (amended: 12-FEB-2001) (amended: 3-MAY-2002) (amended: 11-JULY-2002) (amended: 20-SEP-2002) (amended: 26 March 2003)

Analysis of data collected during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be presented in an annex. (amended: 20-SEP-2002)

10.5.1 Analysis of demographics

The mean, range and standard deviation of height in cm, weight in kg and of age in weeks will be calculated per group, by country and on pooled data from all countries. The racial, gender composition and feeding criteria will be presented.

10.5.2 Analysis of safety

The overall incidence, with exact 95% CI, of any adverse events (solicited or unsolicited) during the solicited follow-up period will be tabulated by group for each study vaccine dose, for overall study vaccine doses and per subject.

The incidence, with exact 95% CI, of each individual solicited general symptoms, will be calculated by group over the solicited follow-up period, after each study vaccine dose, for overall study vaccine doses and per subject. The same calculations will be done for each individual solicited general symptoms rated as grade 2 or 3 and for each individual solicited general symptoms related to vaccination.

For unsolicited symptoms, the type of symptom will be defined by WHO preferred term which will have been associated to the symptom during the data encoding.

The verbatim reports of unsolicited symptoms will be reviewed by a physician and the signs and symptoms will be coded according to the World Health Organisation's (WHO) Dictionary for Adverse Reaction Terminology. Every verbatim term will be matched with the appropriate WHO preferred term. The percentage of subjects reporting unsolicited symptoms classified by WHO body system/WHO preferred terms within 42 days after any study vaccination will be

tabulated with its 95% CI. Similar tabulation will be done for unsolicited symptoms related to vaccination.

Serious adverse events reported during the study period will be described in detail.

An increase in the incidence of specific symptoms with HRV as compared to, placebo will be explored using a one-sided Fisher Exact test. The comparability of the 3 HRV vaccine groups will also be assessed using 2 sided-Fisher exact test. Statistically significant differences (p-value <0.05) should be interpreted cautiously, because of the number of endpoints, the differences observed in this study are likely to occur by chance alone.

Summary of reactogenicity by country will be performed.

10.5.3 Analysis of immunogenicity

For each treatment group, at each time point that a given antigen is measured (see section 5.5.3):

- Seropositivity/seroprotection rates and their 95% Confidence interval will be tabulated,

- GMTs and their 95% CI will be calculated; these calculations will be performed by taking the anti-log of the mean of the log titre transformations. Antibody titres below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMT calculation;

For the subset of subjects who received 2 doses of HRV or placebo: (amended: 3-MAY-2002)

- Vaccine take 2 months after dose 1 and dose 2 will be calculated by group with their 95 % CI

In addition, for all antigens, the distribution of antibody titers two months after the second dose and at the end of the first efficacy follow-up period ~~final~~ study

visit will be displayed using reverse cumulative curves. (amended: 3-MAY-2002) (amended: 20-SEP-2002)

Difference between each vaccine group and placebo two months after dose 2 will be evaluated with respect to immune response to concomitant vaccination and with respect to vaccine take: (amended: 3-MAY-2002)

- The exact two-sided 95% CI for difference in seropositivity/seroprotection rates/vaccine take between each vaccine group and the placebo group will be calculated.
- The two-sided 95% CI for the ratio of GMTs between each vaccine group and the placebo group will also be computed (using a one-way ANOVA model on the logarithm10 transformation of the titers).

The impact of feeding on the vaccine take will be explored using descriptive summaries according to the 3 feeding criteria defined in section 10.2 and using a logistic regression. Likewise the effect of administering a hepatitis B vaccine at birth on the HB seroprotection will be explored.

For the subset of subjects who received 3 doses of HRV or placebo:
The distribution of antibody titers two months after the second dose (rotavirus only) and after the third dose (all antigens) will be displayed using reverse cumulative curve. (amended: 3-MAY-2002).

Please refer to Appendix L for information on analysis and reporting of results on stool analysis from the subset of 200 subjects participating in the site-specific study in Venezuela. (amended: 10-OCT-2001)

10.5.4 Efficacy analysis

Efficacy in the first efficacy follow-up period (amended: 20-SEP-2002)

The vaccine efficacy rate (VE) for subjects who received 2 doses of HRV vaccine or placebo, expressed as 100% X (1-Relative Risk), will be calculated for pooled

vaccine groups and for each vaccine group, with their 95% CI (see Appendix J for mathematical detail) against: (amended: 12-FEB-2001) (amended: 3-MAY-2002) (amended: 20-SEP-2002)

- any and severe rotavirus gastroenteritis during-the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period,
- rotavirus gastroenteritis due to virus types heterologous to vaccine strain occurring two weeks after dose 2 until the end of the first efficacy follow-up period. (amended: 12-FEB-2001)
- any and severe pure rotavirus gastroenteritis occurring two weeks after dose 2 until the end of the first efficacy follow-up period,
- mixed rotavirus gastroenteritis occurring during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period,
- any hospitalization for rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period,

An episode of gastroenteritis will be classified positive for rotavirus if the stool samples collected during the episode are positive as tested by Rota Ag ELISA.

The primary objective is to demonstrate that pooled HRV vaccine groups can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period, and subsequently that the HRV vaccine with a viral concentration of $10^{5.8}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period, and subsequently that the HRV vaccine with a viral concentration of $10^{5.2}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period, and subsequently that the HRV vaccine with a viral concentration of $10^{4.7}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period. (amended: 12-FEB-2001) (amended: 20-SEP-2002)

The primary objective will be addressed using a hierarchical testing procedure.

The efficacy of the pooled vaccine groups will be first evaluated. If the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the first efficacy follow-up period following vaccination in the pooled HRV groups is statistically significantly lower than in the placebo group (two-sided Fisher Exact test: $p < 0.05$), one will conclude that the efficacy of the pooled HRV vaccine groups in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period has been demonstrated. (amended: 12-FEB-2001) (amended: 20-SEP-2002)

If in addition the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the first efficacy follow-up period following vaccination in the HRV group with a viral concentration of $10^{5.8}$ ffu is statistically significantly lower than in the placebo group (two-sided Fisher Exact test : $p < 0.05$), one will conclude that the efficacy of the HRV vaccine with a viral concentration of $10^{5.8}$ ffu in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period has also been demonstrated. (amended: 12-FEB-2001) (amended: 20-SEP-2002)

And, if in addition the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the first efficacy follow-up period following vaccination in the HRV group with a viral concentration of $10^{5.2}$ ffu is statistically significantly lower than in the placebo group (two-sided Fisher Exact test : $p < 0.05$), one will conclude that the efficacy of the HRV vaccine with a viral concentration of $10^{5.2}$ ffu in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period has also been demonstrated. (amended: 12-FEB-2001) (amended: 20-SEP-2002)

And, if in addition the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the first efficacy

follow-up period following vaccination in the HRV group with a viral concentration of $10^{4.7}$ ffu is statistically significantly lower than the placebo group (two-sided Fisher Exact test: $p < 0.05$), one will conclude that the efficacy of the HRV vaccine with a viral concentration of $10^{4.7}$ ffu in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period has also been demonstrated. (amended: 20-SEP-2002)

The above analysis is based on the underlying assumptions that the period of the follow-up is similar in the 4 groups. These assumptions will be examined by analysing the follow-up times using a Cox proportional-hazard model including the group effect as only regressor.

Additional exploratory analyses will be performed, i.e. efficacy by country, efficacy for seropositive subjects at study entry and efficacy against virus types heterologous to vaccine strain.

For the subset of subjects who receive 3 doses of HRV or placebo:

- the proportion of subjects reporting any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the first efficacy follow-up period will be calculated by group and for pooled vaccine groups. An episode of gastroenteritis will be classified positive for rotavirus if the stool samples collected during the episode are positive as tested by Rota Ag ELISA. (amended: 3-MAY-2002) (amended: 20-SEP-2002)

(amended: 20-SEP-2002)

Efficacy in the second efficacy follow-up period

The vaccine efficacy rate

- from the end of the first efficacy period up to the end of the second efficacy period

- from two weeks post last HRV/placebo dose up to the end of the second efficacy period

will be calculated for the pooled vaccine groups and for each vaccine group, with their 95% CI.

More specifically, this will be done for

- any (severe and hospitalized, respectively) rotavirus gastroenteritis,
- any (severe and hospitalized, respectively) rotavirus gastroenteritis due to G1 types
- any (severe and hospitalized, respectively) rotavirus gastroenteritis due to virus types heterologous to vaccine strain

provided the number of cases is sufficient.

The above analyses will be performed separately for the subgroup of subjects enrolled in the 2-vaccine-dose cohort and the subgroup of subjects enrolled in the 3-vaccine-dose cohort.

10.6 Interim analysis

An interim analysis will be performed to provide early information on dose selection. This analysis will present a descriptive summary of immunogenicity and reactogenicity for the study vaccine as well as immunogenicity data for routine vaccines. No study report will be written for the interim data and results will be strictly controlled. Unblinding at the level of individual data will be restricted to the statistician and the database administrator. (amended: 12-FEB-2001)

An interim analysis on efficacy against any and severe rotavirus gastroenteritis will be performed to obtain early efficacy data. The interim efficacy analysis will be performed during the efficacy follow-up period, when about 70 rotavirus gastroenteritis cases, observed from two weeks after dose 2, are reached. This will allow to demonstrate vaccine efficacy (with LL of 95CI > 0) with 75% power based on the following conservative assumptions: vaccine efficacy (for pooled

HRV vaccine groups) against any rotavirus gastroenteritis is 50%, with an attack rate of 6% in the placebo group. No study report will be written for the interim efficacy data and distribution of the results will be strictly controlled. Unblinding at the level of individual data will be restricted to the statistician and the database administrator. (amended: 11-JULY-2002)

Table 10.6-1 indicates the level of accuracy that can be expected for the interim evaluation of efficacy against any rotavirus and severe rotavirus gastroenteritis above a specific cut-off. (amended: 11-JULY-2002)

Table 10.6-1: Power to get an exact 95% CI for the interim vaccine efficacy analysis (pooled vaccine groups versus placebo) above a specific cut-off (460 evaluable subjects per group, power based on 1.000 simulations using Proc StatXact) (amended: 11-JULY-2002)

% of subjects reporting rotavirus gastroenteritis in the placebo group	% of subjects reporting rotavirus gastroenteritis in pooled vaccine groups	Efficacy (%)	Cut-off
			0%
Any Gastroenteritis			
6%	1.8%	70%	97%
6%	2.4%	60%	89%
6%	3.0%	50%	75%
5%	1.5%	70%	96%
5%	2.0%	60%	86%
5%	2.5%	50%	65%
Severe Gastroenteritis			
3%	0.9%	70%	82%
2%	0.4%	80%	79%
2%	0.6%	70%	60%
2%	0.8%	60%	45%

No adjustment on the alpha or the power will be applied for the final analyses of efficacy.

Another interim analysis will be performed on post-dose 3 data. This analysis will present a descriptive summary of immunogenicity and reactogenicity for the study vaccine as well as immunogenicity data for routine vaccines. No study report will be written for the interim data and results will be kept in house. Unblinding at the level of individual data will be restricted to the statistician and the database administrator. (amended: 3-MAY-2002)

An interim analysis on efficacy against any and severe rotavirus gastroenteritis at the end of the second efficacy follow-up period in Mexico will be performed to obtain early efficacy data. No study report will be written and distribution of the results will be strictly controlled. Unblinding at the level of individual data will be restricted to the statistician and the database administrator. No adjustment on the alpha or the power will be applied for the final analyses of efficacy. Considering an attack rate of 12% for any rotavirus gastroenteritis over the two efficacy follow-up periods, a 60% VE and a sample size of 60 subjects in each group, the power to detect a statistically significant vaccine effect with the pooled vaccine group is 40% (2 sided fisher exact test, alpha=5%) (amended: 26 March 2003)

The results o f interim analyses performed on post-dose 2, interim efficacy data and post-dose 3 data may be presented at scientific conferences and, as required, to the authorities. (amended: 3-MAY-2002) (amended: 11-JULY-2002)

11. Administrative Matters

To comply with Good Clinical Practice important administrative obligations relating to investigator responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled. See Appendix B for details.

12. References

1. Ruuska T and Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for severity of diarrheal episodes. Scand J Infect Dis 1990;22:259-267.

2. Kapikan AZ and Chanock RM. Rotaviruses. In: Field's Virology. Eds. Fields BN, Knipe DM, Howley PM. 3rd ed New York, Raven Press 1996;1657-708.

3. Bernstein DI, Sander DS, Smith VE, Schiff GM, and Ward RL. Protection from rotavirus reinfection; 2 year prospective study. J Infect Dis 1991;164:277-83.

4. Velaquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Cartel-Campbell S, Glass RI, Estes MK, Pickering LK, and Ruiz-Palacios MR. Rotavirus infection in infants as protection against subsequent infections. New Engl J Med 1996;335(14):1022-8.

5. Rennels MB *et al*. Lack of an apparent association between intussusception and wild or vaccine rotavirus infection. Pediatr Infect Dis J. 1998; 17: 924-5.

6. Intussusception among recipients of rotavirus vaccine – United States, 1998-1999. MMWR, July 16, 1999 / 48(27);577-581.

7. Bernstein DI, Smith VE, Sherwood JR et al. Safety and immunogenicity of a live attenuated human rotavirus 89-12 vaccine. Vaccine 1998;16:381-7.

8. Bernstein DI, Sack DA, Rothstein E, Reisinger K et al. Efficacy of live attenuated human rotavirus vaccine 89-12 in infants: a randomised placebo-controlled trial. Lancet 1999;354:287-90.

9. Concepcion N and Frasch NE. (1998). Evaluation of previously assigend antibody concentraitons in pneumococcal polysaccharide reference serum 89SF by the method of cross standardization. Clin. Diagn. Lab. Immunol.; 5(2):199-204.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

10. Quataert SA, Kirch CS, Quackenbush Wiedl LJ, et al. (1995). Assignment of weight-based antibody units to a human antipneumococcal standard reference serum, lot 89-S. Clinical and Diagnostic Laboratory Immunology; 2:590 - 597.

11. Romero-Steiner S, LiButti D, Pais LB, et al. (1997). Standardization of an opsonophagocytic assay for the measurement of functional antibody activity against Streptococcus pneumoniae using differentiated HL-60 cells. Clinical and Diagnostic Laboratory Immunology; 4:415.

12. Granström M, et al. (1987). Acellular Pertussis Vaccine in Adults: adverse reactions and immune response. Eur J Clin Microbiol; 6 (1):18-21.

13. Karpinsky KF, et al. (1987). Statistical considerations in the quantitation of serum immunoglobulin levels using the enzyme-linked immunosorbent assay (ELISA). J Immunol Methods; 103:189-194.

14. Sato Y, et al. (1982). Role of antibody to filamentous hemagglutinin and to leukocytosis promoting factor-hemagglutinin in immunity to pertussis. In: Robbins JB, Hill JC, Sardoff JC ed. Seminars in Infectious Disease: Bacterial Vaccines. New-York: Thierne-Strattton, Inc. 1982;380-385.

15. Camargo ME, et al. (1984). Immunoenzymatic assay of anti-diphtheric toxin antibodies in human serum. J Clin Microbiol; 20 (4):772-774.

16. Melville-Smith ME, et al. (1983). A comparison of enzyme-linked immunosorbent assay (ELISA) with the toxin neutralization test in mice as a method for the estimation of tetanus antitoxin in human sera. J. Biol. Standard; 11:137-144.

17. WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines. Combined immunization of infants with oral and inactivated poliovirus vaccines: results of a randomized trial in the Gambia, Oman and Thailand. Bulletin of the World Health Organization, 1996, 74 (3): 253-268.

18. Bergeson PS, Singer SA, Kaplan AR. (1982). Intramuscular injections in children. Pediatrics; 70: 944-948.

19. Ward RL, Bernstein DI, Young EC, Sherwood JR, Knowlton DR, Schiff GM, (1986). Human rotavirus studies in volunteers: determination of infectious dose and serological response to infection. J Infect Dis 154:871-880.

20. Gouvea V, Glass RI, Woods P, Taniguchi K, Clark HF, Forrester B, Fang ZY, (1990). Polymerase chain reaction amplification and typing of rotavirus nucleic acid from stool specimens. J Clin Microbiol 28:276-282.

21. Bergeson PS, Singer SA, Kaplan AR, (1982). Intramuscular injections in children. Pediatrics 70: 944-948.

22. Cook SM, Glass RI, LeBaron CW, Ho MS, (1990). Global seasonality of rotavirus infections. Bull. WHO 68:171-177.

23. White SJ and Freedman LS, (1978). Allocation of patients to treatment groups in a controlled clinical study. Br J Cancer 37:849-857.

Appendix A: World Medical Association Declaration of Helsinki

Recommendations guiding physicians
in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly
Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
41st World Medical Assembly
Hong Kong, September 1989
and the
48th General Assembly
Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the

sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of research, even though the subject has given his or her consent.

Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical research)

In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

The refusal of the patient to participate in a study must never interfere with the physician–patient relationship.

If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

The Physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

Appendix B: Administrative Matters

I. Responsibilities of the Investigator

To ensure that he/she has sufficient time to conduct and complete the study and has adequate staff and appropriate facilities which are available for the duration of the study and to ensure that other studies do not divert essential subjects or facilities away from the study at hand.

To submit an up-to-date curriculum vitae and other credentials (e.g. medical license number in the United States) to the sponsor and—where required—to relevant authorities.

To acquire the normal ranges for laboratory tests performed locally and, if required by local regulations, obtain the Laboratory License or Certification.

To retain no clinical samples (including serum samples) on site without the approval of SmithKline Beecham Biologicals and the express written informed consent of the subject and/or the subject's legally authorized representative.

To perform no other biological assays at the investigator site except those described in the protocol or its amendment(s).

To prepare and maintain adequate case histories designed to record observations and other data pertinent to the study.

To conduct the study in compliance with the protocol and appendices.

To cooperate with a representative of SmithKline Beecham Biologicals in the monitoring process of the study and in resolution of queries about the data.

II. Protocol Amendments and modifications

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

No changes to the study protocol will be allowed unless discussed in detail with the SmithKline Beecham Biologicals' Clinical Project Manager and filed as an amendment/modification to this protocol.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Any amendment/modification to the protocol will be adhered to by the participating center(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments is required prior to implementation; modifications are submitted to IRBs/IECs for information only.

III. Sponsor's Termination of Study

SmithKline Beecham Biologicals reserves the right to discontinue the clinical study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be tendered.

IV. Case Report Form Instructions

Prior to entering the first data each authorised individual will receive a sealed personnel envelope with the user ID and the password. If the authorised individuals should change during the study, the investigator is to inform SmithKline Beecham Biologicals.

Computers with installed electronic CRF (and subject diary cards, if applicable) will be supplied by SmithKline Beecham Biologicals for encoding all data. If appropriate, a printer will also be provided to the investigator. It is the responsibility of the investigator or co-investigator to ensure that the electronic CRF and subject diary cards are legible and that the electronic CRF details are completely encoded.

Errors already transmitted to the central database must be corrected by the authorised individual logged to the electronic CRF via the personal user ID and password.

When a subject completes a visit, it is anticipated that relevant sections of the electronic CRF will be completed by the investigator (or designated staff) within 24 hours of the last data becoming available, but in no case later than 5 days. Similarly, when a subject completes a study, it is anticipated that all relevant CRF screens will be completed within 24 hours of the last data becoming available, but in no case later than 5 days.

This also applies to forms for potential study participants who were screened but not randomised to a study group.

As soon as the subject has completed/withdrawn from the study and the electronic CRF is completed the principal investigator or designated physician(s) under his/her supervision will log-in with his/her personal user ID and password and confirm the screens. Since a direct phone link exists between the user and the database, the password and ID will be considered an electronic signature.

An electronic CRF or log sheets must be submitted for all subjects who have undergone protocol specific procedures, whether or not the subject completed the study.

While completed electronic CRFs will be reviewed by a SmithKline Beecham Biologicals professional monitor at the study site, errors detected by subsequent in-house electronic CRF review may necessitate clarification or correction of errors and documentation and approval by the investigator. Wherever possible the investigator should assist in clarification or correction of errors detected after study finalisation within 48 hours of their being brought to the attention of the investigator.

Any questions or comments related to the electronic CRF should be directed to the assigned Site Monitor.

V. Monitoring by SmithKline Beecham (i.e. the Sponsor)

Monitoring visits by a professional representative of the sponsor will be scheduled to take place before entry of the first subject, during the study at appropriate intervals and after the last subject has completed. It is anticipated that monitoring visits will occur at a minimum frequency of once every eight weeks.

These visits are for the purpose of confirming that SmithKline Beecham Biologicals sponsored studies are being conducted in compliance with the

relevant Good Clinical Practice regulations/ guidelines, verifying adherence to the protocol and the completeness and exactness of data entered on the CRF/RDE screens and Vaccine Inventory Forms. The monitor will verify CRF/RDE entries by comparing them with the source data/documents that will be made available by the investigator for this purpose. Data to be recorded directly into the CRF/RDE screens will be specified in the source documentation agreement form that is contained in both the monitor's and investigator's study file. In cases of RDE, the monitor will mark completed and approved screens at each visit. At the end of the monitoring visit, the monitor will transmit the electronic data. The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits.

VI. Archiving of Data

The investigator/ institution should maintain all study documentation until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of the clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The investigator/ institution should take measures to prevent accidental or premature destruction of these documents. In studies which employ Remote Data Entry, these data will be will be in the CD Rom format.

Similarly, the sponsor-specific study documentation should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational

product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or if needed by the sponsor. The sponsor should inform the investigator/institution in writing of the need for record retention and should notify the investigator/institution in writing when the study-related records are no longer needed.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for SmithKline Beecham Biologicals or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an investigator signs the protocol, he agrees to permit Drug Regulatory Agency and SmithKline Beecham Biologicals' audits, providing direct access to source data/ documents. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application.

SmithKline Beecham Biologicals has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of vaccine development. SmithKline Beecham Biologicals has a Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that SmithKline Beecham Biologicals sponsored studies are in accordance with the Good Clinical Practices and that relevant regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take 1 to 2 days. The SmithKline Beecham Biologicals audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation

required to be maintained, and checks on vaccine accountability. The SmithKline Beecham Biologicals audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring SmithKline Beecham Biologicals of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- IRB/IEC approval
- Vaccine accountability
- Approved study protocol and amendments
- Informed consent of the subjects (written or witnessed oral consent)
- Medical records supportive of eCRF data
- Reports to the IRB/IEC and the sponsor
- Record retention.

SmithKline Beecham Biologicals will gladly help investigators prepare for an inspection.

VIII. Confidentiality and Publication

You agree that all information communicated to you by SmithKline Beecham Biologicals is the exclusive property of SmithKline Beecham Biologicals and you will ensure that the same shall be kept strictly confidential by you or any other person connected with the work and shall not be disclosed, either orally or in written form, by you or such person to any third party without the prior written consent of SmithKline Beecham Biologicals. You shall communicate the results of the work promptly to SmithKline Beecham Biologicals.

We agree that you shall have the right to publish or permit the publication of any information or material relating to or arising out of the work after prior submission to us provided that if we shall so request you will delay publication for a maximum of six months to enable us to protect our rights

in such information or material. Any proposed publication or presentation (e.g. manuscript, abstract or poster) for submission to a journal or scientific meeting, should be sent to the Site Monitor prior to submission, together with confirmation that any other author(s) has seen and agreed the proposed publication/presentation. SmithKline Beecham Biologicals will undertake to comment on such documents within four weeks.

All rights and interests worldwide in any inventions, know-how or other intellectual or industrial property rights which arise during the course of and/or as a result of the clinical study which is the subject of this Protocol or which otherwise arise from the information or materials supplied under this Agreement, shall be assigned to, vest in and remain the property of SmithKline Beecham plc.

Appendix C: Overview of the recruitment plan

- The study will be a multicenter study conducted in Brazil, Mexico and Venezuela. The enrolment in Mexico will be terminated by end December 2001 to avoid vaccinating subjects during the rotavirus season. Thus, no further subjects will be enrolled in Mexico after December 31, 2001. Enrolment of eligible subjects will continue in Venezuela and Brazil to compensate the lower recruitment in Mexico. (amended: 11-DEC-2001)
- Target enrollment was planned at 2640 subjects. Final enrolment is 2276 subjects enrolled as follows: 405 in Mexico, 972 in Venezuela and 899 in Brazil. (amended: 12-FEB-2001) (amended: 11-DEC-2001) (amended: 3-MAY-2002)
- For the subjects who participate only in the first year of efficacy follow-up (until age 12 months), the intended duration of the study, per subject, will be approximately 10 months for subjects. For the subset of subjects who participate in a second efficacy follow-up ***period*** (until ***maximum*** age 24 months), the intended duration of the study, per subject, will be 22 months ***at most***. (amended: 26 March 2003) **(amended: 21 August 2003)**
- The recruitment will be monitored by the site monitor.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Appendix D: Handling of Biological Samples Collected by the Investigator

Instructions for Handling of Serum Samples

When materials are provided by SmithKline Beecham Biologicals, it is mandatory that all clinical samples (including serum samples) be collected using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement.

Instructions for Handling of Serum Samples

1. Collection

The whole blood (by capillary or venous route) should be collected observing appropriate aseptic conditions. It is recommended that Vacutainer® tubes WITH integrated serum separator (e.g. Becton-Dickinson Vacutainer® SST or Corvac® Sherwood Medical) be used so as to minimize the risk of hemolysis and to avoid blood cell contamination of the serum when transferring to standard serum tubes.

2. Serum separation

These guidelines aim to ensure high quality serum by minimizing the risk of hemolysis, blood cell contamination of the serum or serum adverse cell toxicity at testing.

- For separation of serum using Vacutainer® tubes, the instructions provided by the manufacturer should be followed. Siliconized tubes should never be used (cell toxicity). Often the manufacturer's instruction states that the relative centrifugal acceleration known also as "G" must be "between 1000 and 1300 G" with tubes spinning for 10 minutes. Error in calculation of centrifuge speed can occur when laboratory personnel

confuse "G" acceleration with "RPM" (revolutions per minute). The speed of centrifugation must be calculated using the "G" rate provided in the manufacturer's instructions and the radius of the centrifuge head. After measuring the radius of the centrifuge machine, a speed/acceleration nomograph must be employed to determine the centrifuge speed in "RPM".

- Following separation, the serum should be aseptically transferred to the appropriate standard tube using a sterile disposable pipette. The serum should be transferred as gently as possible to avoid blood cell contamination. Only one aliquot should be prepared.
- The tube should not be overfilled (max. 3/4 of the total volume) to allow room for expansion upon freezing.
- The tube should be identified by the appropriate, provided label (see point 3).

3. Labelling

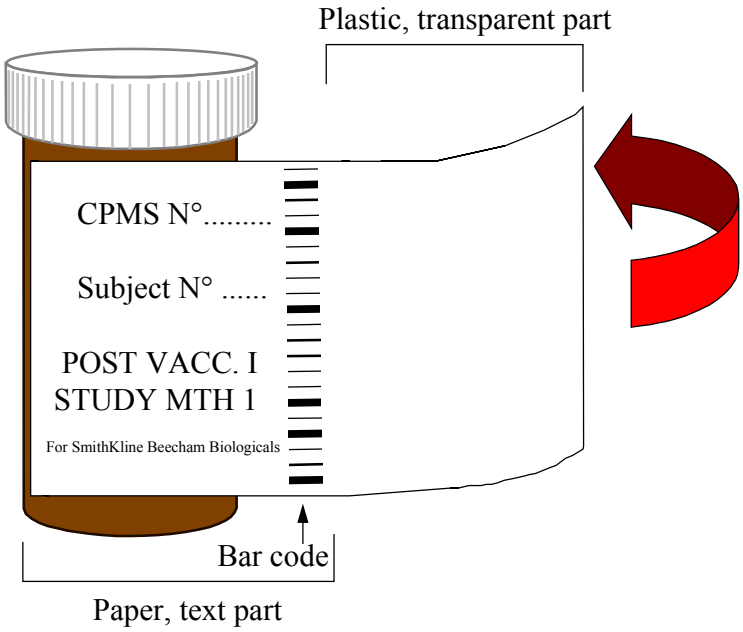
The standard labels provided by SmithKline Beecham Biologicals should be used to label each serum sample.

If necessary, any hand-written additions to the labels should be made using indelible ink.

The label should be attached to the tube as follows (see diagram):

- first attach the paper part of the label to the tube
- then wrap the label around the tube so that the transparent, plastic part of the label overlaps with the label text and bar code and shields them.

This will ensure optimal label attachment.



Labels should not be attached to caps.

4. Sorting and storage

Tubes should be placed in the SmithKline Beecham Biologicals carton or cardboard box in numerical order from left to right, starting from the lower left hand corner, beginning with the pre vaccination samples series, then with the post vaccination sample series.

The tubes of serum should be stored in a vertical position at a temperature between -20°C and -70°C until shipment to core laboratory(ies). Wherever possible, a backup facility for storage of serum samples should be available. (amended: 12-FEB-2001)

Instructions for Handling of Stool Samples

Parents/guardians should use the containers provided by the sponsor to collect stool samples. If not possible, soiled diapers should be individually placed in the ziplock bags and sealed. The date of collection should be written on the container/ziplock bag label with a black ink or ballpoint pen.

The stool specimens will be processed by the investigator's laboratory into stool suspensions and then stored at a temperature between -20°C and -70°C until shipment to core laboratory(ies). (amended: 12-FEB-2001)

Appendix E: Shipment of Biological Samples

Instructions for Shipment of Stool and Serum Samples

Stool and serum samples should be sent at regular intervals. The frequency of shipment of samples should be decided upon by the Site Monitor, Clinical Study Management and the investigator prior to the study start.

Stool and serum samples should always be sent by express air, preferably on a Monday, Tuesday or Wednesday, unless otherwise requested by the sponsor.

Stool and serum samples are enclosed in sealed plastic bag(s) and placed with dry ice (-20°C) in a container complying with IATA requirements. Copies of the completed Serum and Stool Listing Form, and Specimen Transfer Form should be placed in a separate sealed plastic bag and included in the shipment. (amended: 3-MAY-2002) (amended: 11-JULY-2002)

The container must be clearly identified with the labels provided by SB Biologicals specifying the shipment address and storage conditions (-20°C).

A listing form, specifying the samples being shipped for individual subjects at each timepoint, should be prepared for each shipment. The listing identifying the stool samples should detail the date and time of each stool collection: the month should be written using the first 3 letters. A copy of this list should be retained at the study site, while the original should be sealed in a plastic envelope and shipped with the biological samples to the address below. Once flight details are known, a standard Specimen Transfer Form must be completed and faxed to SmithKline Beecham Biologicals to the number provided below. A copy of the Specimen Transfer Form must be in the parcel.

Ship frozen serum/stool samples to:

The investigator will coordinate the shipment of samples to a core laboratory to be determined. (amended: 12-FEB-2001)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Appendix F: Laboratory Assays

1.0 Description of Clinical Immunological Assays

1.1 Measurement of IgA Antibodies by ELISA

This assay allows detection of rotavirus IgA in human serum and was initially designed up by R. Ward [7,8] and adapted by SB Bio. It will be used for estimating the immune response after vaccination and/or infection. Samples will be analyzed in SB Biologicals' in Rixensart, Belgium and/or Dr. [redacted] laboratory in Cincinnati, Ohio.

1.1.1 Description of the ELISA Assay

IgG to rotavirus purified from rabbit serum by affinity chromatography (Pierce Immunopure IgG Purification Kit) captures rotavirus antigen on the solid phase. Rabbit serum, obtained from five rabbits or equivalent, immunized with purified rotavirus, is coated on microplate wells at a ad-hoc concentration (100µl/well). After overnight incubation, the wells are washed and coated antibodies are reacted with either MA104 cell lysate infected with 89-12 strain or equivalent (positive wells) or uninfected MA104 cell lysate or equivalent (negative wells), at 50µl/well ad-hoc concentration. Following incubation on a rotating platform (60 minutes, 37°C), the plates are washed and the dilutions of serum samples or standard are incubated in both kinds of wells (positive and negative) (50µl/well). The use of negative wells allows the assessment of the background for each sample (non-specific binding).

During the reaction time (60 minutes, 37°C under agitation), immunoglobulins to rotavirus are captured by bound viral lysate. The plates are washed and human IgA is detected by addition of biotinylated rabbit anti-human IgA at an optimal concentration (50µl/well, 30 minutes at 37°C under agitation). After washing the plates, 50µl of peroxidase-conjugated avidin at an optimal concentration is added to each well and incubated (30 minutes, RT under agitation). Plates are again washed and 50µl of ad-hoc concentration of orthophenylenediamine (OPD) are

added per well. The plates are then incubated (30 minutes, room temperature (RT) in darkness) before the reaction is stopped with 100µl/well of 2N H_2SO_4.

Coloration is measured at 490 nm. Specific optical densities are calculated for each sample / standard by measuring the difference between positive and negative wells. Specific optical densities of the standard dilutions generate a standard curve using a 4-parameter logistic function. The four-parameter logistic function describes with a high degree of accuracy a standard curve displaying a pronounced sigmoidal shape when plotted on an optical density-versus-log concentration scale. Concentration of the samples is determined by interpolation of OD values on a defined region of the standard curve. In order to use the most accurate part of the standard curve for the calculation of the results, a range of acceptable OD is defined: acceptable test sample ODs must lie between two specified percentages of the upper limit of the standard curve. Antibody concentration in units per milliliter (U/ml) is determined relative to the standard (concentration=1000U/ml) by averaging the values for each unknown that fall within the working range of the standard curve and then correcting for the dilution factor. Each experiment includes negative and positive controls.

1.2 Antigen Detection in Stool Samples

The rotavirus antigen (ROTA Ag) assay detects the presence of ROTA Ag in stool samples. As the small intestine is the site of rotavirus infection, the vaccine must reach this site in order to elicit an immune response. Presence of vaccine / virus in the intestine, indicating a productive infection, may be detected by the ROTA Ag assay. Stool samples are collected from the subjects; suspensions of the stools are tested with the assay. If there is shedding of the vaccine virus in case of undetectable serum IgA, then the subject will be considered as a responder (i.e. vaccine take). Additionally, the test may be used for detecting rotavirus infection associated with gastroenteritis episodes.

The assay designed by R. Ward et al. [**7**,8] was used as the basis for the current SBBio assay method.

1.2.1 Description of the Antigen Detection Assay

Rabbit IgG (DAKO B218), raised against a pool of purified human group A rotaviruses or equivalent, is coated on microplates (positive wells) (100µl/well of an optimal concentration). As control (measurement of background), different wells are coated with non-specific purified Rabbit IgG Fraction (Normal) (DAKO X903) or equivalent (negative wells) (100µl/well of a determined concentration). After an overnight incubation at 4°C, plates are washed and stool suspensions (50µl/well) of the unknown and reference samples are incubated in both kinds of wells. Following incubation on a rotating platform (60 minutes, 37°C), the wells are washed and blocked with 50µl of an optimal concentration of a normal goat serum (15 minutes, RT). Then, guinea-pig antibody (50µl, ad-hoc concentration) to purified double-layered human rotavirus (Wa strain) or equivalent is added for 30 minutes incubation at RT to detect bound ROTA Ag.

After washing the plates, guinea pig antibody specifically fixed on the wells is detected by addition of an optimal concentration of a biotinylated goat anti-guinea-pig immunoglobulin or equivalent (50µl/well) for 30 minutes at RT).

The plates are again washed and 50µl/well of an optimal concentration of peroxidase-conjugated avidin or equivalent are added and incubated (30 minutes, RT). The wells are washed and 50µl of ad-hoc concentration of OPD or equivalent is added per well. After an incubation step of 15 minutes at RT in darkness, the reaction is stopped with 100µl/well of 2N H_2SO_4. Coloration is measured at 490 nm.

A ratio is calculated for each sample (positive well/negative well); the ratio is compared to a threshold. Samples whose ratios are found above the threshold are considered positive while samples with ratios lower than the threshold are considered negative. Each experiment includes a positive reference sample.

1.2.2 Antigen Detection in GE Stool Samples (amended: 12-FEB-2001)

A rapid screening will be performed at the study sites to determine the presence of rotavirus in the stool using a commercial test (Rotaclone or equivalent).

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Additional testing for other pathogens is done on rotavirus positive GE stool samples during the first year of efficacy follow-up, but not during the second efficacy follow-up ***period***, as described in section 5.5.2. (amended: 12-FEB-2001) (amended: 26 March 2003) **(amended: 21 August 2003)**

1.3 The Reverse Transcriptase Polymerase Chain Reaction Method

1.3.1 Detection of Rotavirus by PCR in Stool Samples

The confirmation of rotavirus from clinical samples will be performed by using the RT-PCR method.

This particular RT-PCR uses primers which in a first round of amplification generate a full length copy of the VP7 gene from any group A rotavirus strain, as described by Gouvea et al.[20].

The first amplification is performed with the primer pair Beg9 and End9. The reaction produces a DNA fragment of 1063 bp length which is visualized on an ethidium bromide-stained agarose gel.

1.3.2 Typing of Rotavirus Polymerase Chain Reaction

The typing of rotavirus from clinical samples will be performed by a second round of amplification.

The typing PCR uses a cocktail of primers specific to the VP7 gene to generate PCR fragments of different sizes specific for G1, G2, G3, G4, and G9 types, as described by Gouvea et al. [20].

The typing PCR is performed with a pool of type-specific primers aBT1, aCT2,aET3, aDT4, aFT9 (variable regions of VP7 gene) that anneals to the 5' end of the VP7 gene and a common primer RVG9 that anneals to the 3'end.

The amplification reaction produces a fragment length characteristic for each type which is visualized on ethidium bromide-stained agarose gel.

1.3.3 Differentiation of G1 Vaccine Strain From G1 Wild Type Strain

To differentiate G1 vaccine strain RIX4414 from G1 wild-type strains, different approaches can be envisaged using the G1 VP7 gene fragment generated by the RT-PCR typing assay (by Slot Blot hybridization , by sequencing).

Appendix G: Vaccine Supplies, Packaging and Accountability

It is under no circumstances permitted to use supplies for purposes other than those specified in the protocol. Unused supplies will be collected by the sponsor on completion of the study. Used vaccine vials can be disposed on site according to local biosafety standards for disposal of biological waste material.

Vaccine supplies

The investigators will be supplied by the sponsor with the appropriate amounts of numbered doses of study vaccines needed to fulfill their enrollment goal. The following represents the total amount of numbered doses of study vaccines, sufficient to administer the appropriate number of doses to all subjects as described in the present protocol:

- 1452 doses of the $10^{4.7}$ HRV vaccine
- 1452 doses of the $10^{5.2}$ HRV vaccine
- 1452 doses of the $10^{5.8}$ HRV vaccine (amended: 12-FEB-2001)
- 1452 doses of the placebo
- 5808 doses of the diluent
- 7920 doses of DTPw-HB+Hib vaccine
- 7920 doses of *Polio Sabin*

An additional 5% of HRV/placebo doses, DTPw-HB+Hib vaccine and *Polio Sabin* will be supplied for replacement in case of breakage or bad storage conditions.

The following represents the vaccine supplies that will be provided to administer the third dose of study vaccine/placebo to the subset of 200 subjects including 20% over-randomisation:

- approximately 60 doses of the $10^{4.7}$ HRV vaccine
- approximately 60 doses of the $10^{5.2}$ HRV vaccine

- approximately 60 doses of the $10^{5.8}$ HRV vaccine
- approximately 60 doses of the placebo
- 240 doses of the diluent (amended: 3-MAY-2002)

All vials need to be accounted for on the form provided.

Vaccine packaging

The double-blind vaccines will be packed in labelled boxes. The box label will contain the following information: study number, subject number, lot number (or numbers, when double blind), instructions for vaccine administration.

Vaccine accountability

The investigator or pharmacist must sign a statement that he/she has received the clinical supplies for the study. The statement should contain the assurance that investigational products will be handled and stored safely and properly; that investigational products will only be dispensed to study subjects/patients in accordance with the protocol; that any unused vaccine (including placebo) will be returned to SmithKline Beecham Biologicals. At any time the figures on supplied, used and remaining vaccine doses should match. At the end of the study, it must be possible to reconcile delivery records with those of usage and returned stocks. Account must be given of any discrepancies. Certificates of returns must be signed with the assurance from investigator/pharmacist that all unused dosage forms (vaccine and placebo) for the stated study have been returned- including all opened and unopened packages.

Labels for sample identification

The investigator will receive labels to identify samples taken from each subject at each timepoint. The label will contain the following information: study number, subject number, sampling timepoint, timing.

Other supplies provided by the sponsor

In addition to the vaccines, the study documentation and the sample labels, the investigator will receive the following supplies:

- tubes with screw caps for serum samples
- racks for the tubes of serum
- digital thermometers
- containers/ziplock bags to be given to the parent/guardian for collection of stool samples

Appendix H: Sample Subject Information and Informed Consent

(FOR ALL STUDY PARTICIPANTS)

Study title: A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Investigator:

Sponsor : SmithKline Beecham Biologicals

CPMS protocol number: 4444563/006 (Rota-006)

Date of Approval: October 20, 2000 – Final protocol

February 12, 2001 – Amendment 1

May 14, 2001 – Modification

October 10, 2001 – Site-specific amendment

December 11, 2001 – Amendment 2

May 3, 2002 – Amendment 3

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

July 11, 2002 – Amendment 4

September 20, 2002 – Amendment 5

Prepared by : [redacted] R.Ph.

Amendment 3 dated May 3, 2002, did not result in any changes to the Appendix H. Refer to Appendix M for supplemental consent for subjects who will receive three doses of study vaccine or placebo.

CLINICAL RESEARCH AND DEVELOPMENT

SmithKline Beecham Biologicals

This document should be presented to the parent/guardian of the subject in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the participant.

1. Introduction

In order to decide whether your child should be in this research study, you should know about the study's risks and benefits. Then you can make an informed decision. This consent form gives you detailed information about the study. A member of the research team will discuss all of this information with you. He or she will explain the study's purpose, procedures to be performed, any risks and discomforts of the study, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you want your child to be in the study. If you do, you will be asked to sign this form.

This consent form may contain words that you do not understand. Please ask the study doctor or staff to explain anything unfamiliar.

You will receive a signed copy of this consent form for your records.

The rotavirus disease

Most of the world's population is poor and lives in developing countries. In developing countries, rotavirus gastroenteritis is an enormous problem. World-wide, 60-80 young children with rotavirus gastroenteritis die every hour. The only practical solution to control this global health problem is a rotavirus vaccine for infants. Yet today, there is no rotavirus vaccine available anywhere.

Protection against disease

Several rotavirus vaccines have been tested for infants. In August 1998 a rotavirus vaccine, RotaShield™, became available in the USA. In large research studies, the vaccine prevented 90% of severe rotavirus gastroenteritis and worked so well that few vaccinated children had to stay in the hospital for treatment of rotavirus dehydration.

Nevertheless, after about 1 year in which almost 1 million infants were vaccinated, the vaccine manufacturer stopped selling the vaccine. Why? Because the Public Health Service discovered that infants receiving the RotaShield™ vaccine were getting a kind of intestinal blockage called intussusception. Intussusception normally occurs in about 1 in 3000 infants. But among infants who got RotaShield™, it occurred almost twice as commonly. The intussusception occurred mainly 1-2 weeks after the vaccination. What is intussusception? Intussusception is when a length of small intestine enfolds inside the intestine next to it (like a collapsible telescope). The enfolded intestine creates a blockage that unless treated, can rupture, causing severe infection, shock and sometimes death. Because the RotaShield™ vaccine seemed to be causing intussusception, the manufacturer stopped selling it.

SmithKline Beecham Biologicals has now developed a new investigational rotavirus vaccine. The SmithKline Beecham vaccine is based on a human rotavirus. The human rotavirus in the new vaccine has been weakened so that when a child swallows it, it causes only a mild infection with few to no symptoms. The child is expected to become immune from the weakened human rotavirus infection.

The SmithKline Beecham human rotavirus vaccine is different from RotaShield™ vaccine which was based on a live rotavirus from monkeys. As we said above, almost all children get infected with human rotavirus, but they don't get intussusception. Most experts believe that natural rotavirus infections cause very few cases of intussusception among infants. You should understand that the actual safety of this investigational vaccine will be unknown until extensive tests are finished. The safety tests done so far are described below.

The study doctor and/or the institution where the study is taking place is being paid by the sponsor (SmithKline Beecham) to conduct this study.

2. Description/Purpose of the Study

This is a medical research study. The study's purpose is to further test how infants respond to the human rotavirus vaccine. Healthy infants who have never had rotavirus infection will swallow the rotavirus vaccine twice, 2 months apart, when they get their routine vaccinations. We will look for side effects (like fever, loss of appetite, fussiness/irritability, vomiting, diarrhea [three or more looser than normal stools within a day] and runny nose/cough). We will take blood and stool (poop) samples to see how your child's immune system (part of body that fights infection) reacts to the investigational vaccine. To see if any side effects that occur are related to the rotavirus vaccine, some infants will get a placebo (looks like vaccine but has no activity) instead of rotavirus vaccine. Neither you nor your doctor will know whether your child got the placebo until the end of the study. (amended: 12-FEB-2001)

We will test the human rotavirus vaccine at 3 different strengths. Various strengths of the investigational rotavirus vaccine have been tested already in more than 200 infants and previously an earlier version of the vaccine made by another manufacturer was tested in approximately 200 infants. Those tests found no safety problem with the vaccine and they showed that the earlier vaccine really prevented rotavirus gastroenteritis. (amended: 12-FEB-2001)

After your child is vaccinated, we will see whether the human rotavirus vaccine prevents any and severe rotavirus gastroenteritis. We will diagnose rotavirus gastroenteritis by collecting stool samples from infants that develop gastroenteritis (diarrhea). We will test the stool samples for rotavirus and some other pathogens. We will see the number of rotavirus gastroenteritis cases in the group of infants that got human rotavirus vaccine compared to the group that got placebo. (amended: 12-FEB-2001).

This study will be conducted in Brazil, Mexico and Venezuela so that 2640 infants, 6 to 12 weeks of age, can enter the study. Infants that enter the study will complete the study when they are 1 year of age.

In this study, your child will get the investigational human rotavirus vaccine or placebo at the same time that he or she gets routine vaccines recommend by the Expanded Program on Immunizations (EPI).

3. Approval

The study was reviewed and accepted by an Independent Ethics Committee.

4. Study Participation and Study Procedures

Your child can not join the study if he or she is taking some kinds of medicines or has certain medical conditions. Study personnel will ask you about this.

Once the study staff sees that your child is eligible to join the study, you will be asked to read this informed consent document. If you sign the consent form, your child can join the study. If you join, your child will have a physical examination when he or she comes to get routine 2 month vaccines (at 6-12 weeks of age). Also at that appointment, study personnel will ask you questions about your child's medical history and medicines that your child may be taking. For a subset of 400 subjects enrolled, we will collect a stool sample on the day of vaccination. We will collect a stool sample on the day of vaccination. We will draw a blood sample from your child. (amended: 12-FEB-2001)

Your child will be randomly put (like flipping a coin) into one of four groups, with a 3 out of 4 chance of receiving the investigational human rotavirus vaccine and a 1 out of 4 chance of receiving a placebo. Your child will receive the vaccine or placebo at 2 and 4 months of age by mouth. To make a strong but fair test of the investigational human rotavirus vaccine, neither you nor the study staff will know who gets vaccine or the placebo. But if necessary during the study, your doctor can have this information.

All infants will receive separate injections of routine vaccines recommended by the EPI.

Oral polio vaccine will be given 2 weeks apart from the study vaccine/placebo.

The quantity of the stool sample should be at minimum 2 spoons (the spoon is within the stool container) and at maximum half of the container. Write the name, date of collection on the container label with a black ballpoint pen. A field worker will collect the stool samples. (amended: 12-FEB-2001)

If you live in Venezuela, you may be asked to collect 10 additional stool samples from your child for further testing of your child's response to the vaccine. This additional testing will be performed in 200 infants. (amended: 10-OCT-2001)

It is expected that your child will participate in the study for approximately 10 months. A Health Worker will visit your child every week (except for weeks when a study clinic visit is scheduled) until your child reaches one year of age.

There will be a total of 4 study visits.

Visit 1 (2 months of age):

- You will be asked questions about your child's health, your child will be examined by the doctor and his/her temperature will be taken. You will be asked to provide a stool sample if your child is one of 400 infants selected for stool tests. This stool sample will be tested for rotavirus. (amended: 12-FEB-2001)

- There will be no restriction on feeding your child.
- A blood sample (1ml) will be collected from your child.
- Administration of study vaccine/placebo:
  - Oral administration of first dose of the study vaccine/placebo
- Administration of routine vaccines: DTPw-HB+Hib vaccine
- After vaccination, your child will be kept under observation for 30 minutes to check for any immediate vaccine reactions
- At the end of the 30 minutes of observation period, you will be given a diary card to record body temperature (measured by axillary or rectal route), the number of looser than normal stools passed by the subject, the number of vomiting episodes, any loss of appetite, any fussiness/irritability, any runny nose/cough during the 15-day solicited follow-up period. Unsolicited symptoms occurring within 42 days after dose 1.
- If your child is one of 400 infants selected for stool tests, you will be asked to collect a stool sample 7 days after vaccination. (amended: 12-FEB-2001)
- If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect a stool sample just before vaccination and 14 and 28 days after vaccination. This stool sample will be used for further testing of your child's response to the vaccine. (amended: 10-OCT-2001)
- For each episode of gastroenteritis, you will be instructed to contact the study site personnel and to daily record the following on a diary card until symptoms resolve: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. You will be asked to collect one stool sample. A second stool sample will be collected on a different day if the first sample was insufficient. (amended: 12-FEB-2001)
- If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect two additional stool samples for each episode of gastroenteritis: one at 1-5 days after onset of symptoms and the second at 14 days after onset of symptoms. (amended: 10-OCT-2001)

Visit 2 (4 months of age):

- A physical examination will be carried out.

- There will be no restriction on feeding your child.
- If your child is one of 400 infants selected for stool tests you will be asked to collect a stool sample on the day of vaccination. (amended: 12-FEB-2001)
- If your child is one of 800 infants selected for blood tests of the vaccine, a blood sample (1ml) will be collected. (amended: 12-FEB-2001)
- Administration of study vaccine/placebo:
  - Oral administration of second dose of the study vaccine/placebo
- Administration of routine vaccines: DTPw-HB+Hib vaccine
- After vaccination, your child will be kept under observation for 30 minutes to check for any immediate vaccine reactions
- At the end of the 30 minutes of observation period, you will be given a diary card to record body temperature (measured by a axillary or rectal route), the number of looser than normal stools passed by the subject, the number of vomiting episodes, any loss of appetite, any fussiness/irritability, any cough/runny nose during the 15-day solicited follow-up period, as well as unsolicited symptoms occurring within 42 days after dose 2.
- If your child is one of 400 infants selected for stool tests, you will be asked to collect a stool sample 7 days after vaccination. (amended: 12-FEB-2001)
- If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect a stool sample just before vaccination and 14 and 28 days after vaccination. This stool sample will be used for further testing of your child's response to the vaccine. (amended: 10-OCT-2001)
- For each episode of gastroenteritis, you will be instructed to contact the study site personnel and to daily record the following on a diary card until symptoms resolve: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. You will be asked to collect one stool sample. A second stool sample will be collected on a different day if the first sample was insufficient. (amended: 12-FEB-2001)
- If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect two additional stool samples for each episode of gastroenteritis: one at 1-5 days after onset of symptoms and the second at 14 days after onset of symptoms. (amended: 10-OCT-2001)

Visit 3 (6 months of age):

- A physical examination will be carried out.
- If your child is one of 800 infants selected for blood tests a blood sample (3mls) will be collected to test the effectiveness of the investigational vaccine and the routine pediatric vaccines. (amended: 12-FEB-2001)
- Administration of routine vaccines: DTPw-HB+Hib vaccine.
- If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect a stool sample every two months from six months of age until Visit 4. (Amended: 10-OCT-2001)
- For each episode of gastroenteritis, you will be instructed to contact the study site personnel and to daily record the following on a diary card until symptoms resolve: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. You will be asked to collect one stool sample. A second stool sample will be collected if the first sample was insufficient. (amended: 12-FEB-2001)
- If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect two additional stool samples for each episode of gastroenteritis: one at 1-5 days after onset of symptoms and the second at 14 days after onset of symptoms. (amended: 10-OCT-2001)

Visit 4 (10 months to 1 year of age):

- A physical examination will be carried out.
- If your child is one of 800 infants selected for blood tests, a blood sample (3mls) will be collected to test the effectiveness of the investigational vaccine and the routine pediatric vaccines. For all other children, a 1 ml blood sample will be taken from your child to determine the effectiveness of the investigational vaccine only. (amended: 12-FEB-2001)

4. Potential Risks Associated with the Study

There are risks if your child enters this study. The risks come from the use of an investigational human rotavirus vaccine and from collection of a maximum of 4 blood samples. These risks are explained below. (amended: 12-FEB-2001)

The investigational human rotavirus vaccine is new. Although it has been given safely to a small number of adults, toddlers, and infants, it may have unknown side-effects. The vaccine is a live rotavirus, therefore it may cause symptoms of gastroenteritis such as fever, loose stools or vomiting.

The vaccine, in spite of careful manufacturing, may contain infectious agents other than rotavirus that may harm your child. There have been extensive tests of all materials that go into the vaccine to reduce this risk. The manufacturing and testing of the human rotavirus vaccine was reviewed by the U.S. Food and Drug Administration. They have agreed the human rotavirus vaccine may be used in a similar research study in the United States.

The human rotavirus vaccine may cause allergic reactions. Allergic reactions to vaccines are quite unusual. Serious allergic reactions are most likely to occur within minutes of swallowing the vaccine. Your child must stay in your doctor's office for 30 minutes after each study vaccine dose so that any reaction can be treated. (amended: 12-FEB-2001)

The human rotavirus vaccine may cause intussusception (blockage in the small intestine). The use of an earlier rotavirus vaccine (RotaShield™) was stopped because it appeared to increase the rate of intussusception. The investigational human rotavirus vaccine is quite different from the RotaShield™ vaccine. Nevertheless, there is the possibility that any rotavirus vaccine may cause intussusception.

Your doctor and the study staff know of the possible risk of intussusception. They have arranged for prompt examination of any child in this study with suspected intussusception. Symptoms of intussusception are severe abdominal pain (colic), persistent vomiting, bloody stools, abdominal bloating and high fever (even up to 41°C). If your child has symptoms of intussusception, you should first contact your investigator and if unsuccessful, take your child immediately to the emergency room. Early diagnosis of intussusception should allow successful treatment as an outpatient in a hospital x-ray department. But if hospital treatment with an air or fluid enema is unsuccessful, abdominal surgery will be

necessary. If your child has intussusception, there is a plan to collect samples (serum, throat swab and stool) in order to enhance our understanding of intussusception. Your doctor can tell you more about intussusception, its treatment, and the suspected link between intussusception and RotaShield™.

If your child is one of 800 infants selected for blood tests, a 1 ml blood sample will be taken at Visits 1 and 2 and a 3 ml blood sample will be taken at Visits 3 and 4. For all other child, we will take a 1 ml blood sample from your child at Visits 1 and 4. This may cause pain and bruising of the skin where the needle is inserted. (amended: 12-FEB-2001)

Your child will receive routine vaccinations recommended by the EPI. These vaccines may cause side effects including pain and swelling at the injection site, high fever, fussiness/irritability, vomiting, and poor feeding**,** and in very rare cases allergic reactions. (amended: 12-FEB-2001)

The human rotavirus vaccine given to your child may reduce the beneficial effect of the routine vaccinations given at the same time. This is possible but very unlikely. Remember that the human rotavirus vaccine and routine vaccines will be given together when your child is 2 and 4 months old. But your child will receive the routine vaccinations alone without human rotavirus vaccine at 6 months of age. If your child is one of 800 infants selected for blood tests, we will test your child's blood for antibody levels expected from the routine vaccines at 6 and 12 months of age. Antibodies are substances made by your child's immune system to prevent infections. Your child's antibody test results will be reported to your doctor. (amended: 12-FEB-2001)

The safety of this research will be monitored by an independent group of pediatricians and experts in vaccination. They will be told of every serious illness occurring in any child in the study. They will have authority to stop the study if they suspect any problem with the investigational human rotavirus vaccine or the way the study is being performed.

You will be informed of anything learned during the study which might affect the well-being of your child.

5. Potential Benefits Associated with the Study

If the vaccine is efficacious, your child may have the benefit of immunity against rotavirus diseases. If the human based vaccine proves to be useful, also other children may benefit from it in the future.

There will be no charge for study-related doctor visits, examinations, and laboratory tests. All vaccines will be provided free of charge.

6. Alternatives

There is no licensed rotavirus vaccine currently available.

Disease caused by rotavirus is treated with oral rehydration solutions or if necessary, intravenous fluid replacement. This is to prevent dehydration and shock. There is no treatment to shorten the illness or to reduce vomiting or diarrhea.

If you decide against joining the study, your child can receive the recommended licensed vaccines as part of their routine care from your usual doctor. The routine immunizations include, DTP vaccine, Hib vaccine, hepatitis B vaccine and polio vaccine.

Joining this study is voluntary. If you decide against joining, there will be no penalty. You and your child will lose no benefits.

7. Confidentiality and Data Access

You understand and consent to the following:

It will be necessary for representatives of SmithKline Beecham or possibly health authorities to access your medical records. Your participation in the study will be treated as confidential, that is, any personally identifiable information will be held and processed under secure conditions at SmithKline Beecham (or an agent of SmithKline Beecham) with access limited to appropriate SmithKline Beecham staff or other authorised agents having a requirement to maintain the confidentiality of the information. You will not be referred to by name in any report of the study. Your identity will not be disclosed to any person, except for the purposes described above and in the event of a medical emergency or if required by law.

Your personal data will be processed electronically to determine the outcome of this study, and to provide it to health authorities. Your data may be transferred to other countries (such as USA) for these purposes SmithKline Beecham complies with internal procedures to protect personal information even in countries whose data privacy laws are less strict than those of this country. The data may also be used for other medical research purposes.

You may be entitled under law to access your personal data and to have any justifiable corrections made. If you wish to do so, you should request this from the doctor conducting the study.

8. Your Right to Ask Questions and/or Withdraw from the Study

You may ask questions about the study. Although your continuous support is appreciated, you have the right to withdraw your child from the study at any time. If you have any questions concerning the study, please contact:

Your child's pediatrician, Dr..... Tel. No.....

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

or,

Name ....Dr..... Tel. No.....

Your doctor may withdraw your child from the study at any time if he or she feels that is in your child's best interest.

If you should withdraw your child voluntarily from the study or are asked by your doctor to withdraw your child from the study, you will be asked questions about your child's experience with the study vaccine. You also may be asked to cooperate in having your child receive whatever laboratory tests and physical examinations your doctor considers necessary.

9. Compensation (Medical/Financial) to be provided

If your child becomes ill or injured as a result of taking part in this clinical study, medical treatment will be provided according to good clinical practice and the reasonable costs of such treatment beyond those paid by your insurance will be paid for by SmithKline Beecham Biologicals. All participants in the study are covered by global insurance policy contracted by SmithKline Beecham Biologicals.

If you have any questions concerning the availability of medical care or if you think your child has experienced a research-related illness or injury, please contact:

Name…… Tel. No……

10. Voluntary Participation

Your and your child 's participation in this study is entirely voluntary.

Your refusal to participate in this study will not involve any penalty or loss of benefits to which your child is otherwise entitled.

You may withdraw from the study at any time without loss of benefits to which your child is otherwise entitled.

Your child 's medical care will not change if either you refuse to have your child participate in this study or you decide to discontinue in this study at any time.

You are entitled to receive a signed copy of this form from the study coordinator.

Consent Statement

This vaccine study has been clearly explained to me and I have read and understood the information provided. I agree that my [son/daughter/ward] be enrolled in the study. I understand that I have the right to decline to enter my [son/daughter/ward] in this study and to withdraw from it at any time for any reasons without consequence to his/her present or future health care and attention that he/she receives from his/her healthcare provider. I have been made aware of my right to access and request correction of my child's/ward's personal data. I acknowledge that I have received a copy of this form for future reference.

I, _____ ,
(subject's parent or legal guardian's first name and family name)

hereby freely give my consent for my child/ward to take part in this [clinical/vaccine] study.

Participant's Name: _____
(First Name, Family Name)

Parent/Guardian's name: _____
(First Name, Family Name)

Parent/Guardian's signature: _____

Relationship to participant: _____

Participant's main address: _____

Participant's phone number: _____

Date: _____ **Time:** _____
(DD-MM-YY)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Name of Consent Presenter: _____

Signature of Consent Presenter _____

Appendix I: Follow-up of intussusception cases

In light of the possible increased risk of intussusception following administration of a previously licensed rotavirus vaccine, the safety of the candidate HRV vaccine will be monitored vigilantly during the clinical studies.

The investigator will be asked to inform the parents/guardians of the signs and symptoms of intussusception. Parents/guardians/caretakers of study subjects will be asked to contact the investigator if they notice any signs or symptoms indicative of intussusception. Symptoms consistent with intussusception are severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41°C. The investigator will be aware of the possible increased risk of intussusception and will consider this diagnosis among children presenting these symptoms. The investigator and his staff will take appropriate actions to treat the condition.

If any case of intussusception should occur during this clinical study, the following procedures will be followed by the investigator for work-up of the intussusception cases.

1. **Case ascertainment**

The diagnosis of intussusception should be documented by radiography. Documentation by ultrasonography will be optional depending on availability of necessary expertise.

2. **Data collection for intussusception cases**

The investigator will document all available information regarding any intussusception cases occurring during the clinical studies on the Serious Adverse Event pages and fax within 24 hours (1 calendar day) of his/her becoming aware of the event to the SmithKline Beecham Contact for Serious Adverse Event (SAE) Reporting. (amended: 12-FEB-2001)

The investigator should follow the same procedures for reporting intussusception cases as for other SAEs.

To allow for a complete assessment of the intussusception cases, information on the subject's feeding practices, immunization history, as well as any other information thought necessary for assessment by the study staff should be reported to the SB safety contact by using the IS reporting form. (amended: 12-FEB-2001)

3. Serum, throat and stool specimen collection from intussusception cases

Idiopathic intussusception is thought to be related to lymphoid hyperplasia in the intestinal sub-mucosa and/or mesenteric adenitis resulting from infections. Infectious agents most clearly linked to intussusception are enteroviruses and respiratory adenoviruses. Human rotaviruses also may cause intussusception, although epidemiologic data suggest this must be very unusual. In theory, any agent able to replicate in the small intestine could provoke this condition.

We will use a central laboratory to perform RT-PCR on throat swabs and stool samples for enteroviruses and adenoviruses and on stool samples alone for rotaviruses. The physician treating a case of intussusception should submit stool samples to the hospital microbiology laboratory for culture of enteric pathogens including Salmonella, Shigella, Campylobacter, and Yersinia. If culture results suggest presence of enteropathogenic *E. coli,* representative colonies should be retained for further evaluation. The samples to be collected and their handling are described below

If possible a stool specimen should be collected just prior to or immediately after the air or contrast enema as well as samples 24 hours and 48 hours after the reduction. The hospital microbiology laboratory should divide each stool specimen into an aliquot for its own testing and two additional aliquots of at least 2 grams each to be frozen at –20°C to –70°C. The frozen stool samples will be used for RT-PCR and other studies to be arranged by SmithKline Beecham Biologicals, such as virus culture, antigen detection by immunoassay, or electron

microscopy for virus-like particles. Accordingly, a complete set of stool specimens will be comprised of 3 specimens submitted for bacterial culture and 6 frozen specimens retained for shipment to SmithKline Beecham Biologicals. In the event that feces are unobtainable at any of the requested sampling times, 3 separate rectal swab specimens should be collected. One swab specimen should be submitted for bacterial culture and the other 2 swabs should be placed each in a separate tube of 2 ml of sterile virus transport media and frozen at –20°C to –70°C. (amended: 12-FEB-2001)

A throat swab should be collected as soon as possible after intussusception is diagnosed. The throat swab should be placed in 2 ml of sterile virus transport media and frozen at –20°C to –70°C. (amended: 12-FEB-2001)

In case of surgical reduction, a surgical specimen of any enlarged mesenteric lymph should be obtained. If bowel or the appendix is resected, these specimens also should be included in the evaluation. If possible, resected tissue should be divided into 3 aliquots to be processed for routine fixation, for electron microscopy (fixation in 4% paraformaldehyde and 1% glutaraldehyde), and for frozen sectioning for detection of virus antigens by immunofluorescence. Routinely fixed specimens should be examined for histopathologic evidence of acute inflammation and presence of virus inclusions or other diagnostic signs. Additional testing including referral of tissue blocks for outside review and/or tests using immunohistochemistry, in situ hybridization, or PCR will be arranged by SmithKline Beecham Biologicals in consultation with the Attending Pathologist.

Acute and convalescent blood (at least 2 ml of each) should be collected and stored at –20°C for serologic testing. These specimens will be supplemented by antecedent serum specimens from the patient already collected under this protocol. Testing will be arranged by SmithKline Beecham Biologicals to detect an acute antibody response to any pathogen identified by stool and/or throat swab tests or by histopathologic evaluation of tissue.

Appendix J: Mathematical details about sample size determination

1. Monotonic transformation between VE and p*

The Vaccine Efficacy (VE) can be estimated by:

$$VE = 1 - \frac{n1/N1}{n2/N2} \approx 1 - \frac{n1}{n2}$$ since N1/N2 ≈ 1 in a 1:1 randomisation ratio

where ni = number of cases in group i
Ni = number of subjects in group i

Conditionally to the total number of cases n = n1+n2, let *p* denote the proportion of cases in group 1,

$$VE = 1 - \frac{n1}{n} * \frac{n}{n-n1} = 1 - p * \frac{1}{1-p} = 1 - \frac{p}{1-p} \qquad (1)$$

where $p = n1/n$ is binomially distributed

There is therefore a monotonic link between VE, the true vaccine efficacy, and p, the true proportion of subjects in group 1 among the total cases in the two groups. 95%CI for vaccine efficacy can then be derived from the exact 95% CI from p.

* Reference to DIA presentation – Sample size considerations for vaccine Trials with Rare Events – on June 2000 by Robert C. Kohberger and Bruce H. Fireman.

Appendix L: Site-specific study of rotavirus specific IgA antibodies in feces in Venezuela

(amended: 10-OCT-2001)

Rationale: Natural rotavirus infection is known to afford clinical protection against subsequent episodes of disease ([2], [3], [4], [5], [6]) and specific IgA in serum and in fecal samples are considered to be good predictors of protection against natural rotavirus illness ([7], [8], [9], [10]).

Fecal rotavirus IgA immune response and the role of IgA antibodies as marker of protection against rotavirus disease will be therefore evaluated in a site-specific study in Venezuela. A subset of 200 infants from Venezuela enrolled in study rota-006 and receiving GSK Biologicals' HRV vaccine or placebo will participate in this site-specific study.

Investigator: This site-specific study will be conducted by Dra. [redacted] the investigator in Venezuela.

Number of Subjects: A subset of 200 infants enrolled in study rota-006 will participate in this site-specific study.

Timepoints for stool samples: Stool samples will be collected on day 0, 14 and 28 after each dose and then every two months from 6 months of age until Visit 4 (10 stool samples per infant) as mentioned below.

Stool sample no.	Vaccination	Day	Month	Age (months)
1	Dose 1	0	0	2
2		14		
3		28	1	3
4	Dose 2	0	2	4
5		14		
6		28	3	5
7			4	6
8			6	8
9			8	10

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

10			10	12

During each gastroenteritis episode occurring during the study period, two additional stool samples will be collected from this subset during acute (1-5 days after onset of symptoms) and convalescent (14 days after onset of symptoms) phase.

Laboratory assays: All additional stool samples collected from the subset of 200 subjects from Venezuela will be tested by ELISA to determine fecal anti-rotavirus IgA antibody levels ([11], [12]). The laboratory tests will be the responsibility of Dra. [redacted] the investigator.

Analysis of results: Analysis and reporting of the data from tests performed on the additional stool samples from the subset of 200 subjects in Venezuela will be the responsibility of Dra. [redacted] the investigator. GSK Biologicals will have access to the data and will review it.

References:

[1] ***World Health Organization. A Standard Verbal Autopsy Method for Investigating Causes of Death in Infants and Children. Geneva: World Health Organizatoin, 1999:1-78. (WHO/CDS/CSR/ISR/99.4).*** **(Amended: 21 February 2003)**

[2] Bernstein DI, Sander DS, Smith VE et al. Protection from rotavirus reinfection: 2-year prospective study. J Infect Dis 1991;64:277-83.

[3] Ward RL, Bernstein DI. Protection against rotavirus disease after natural rotavirus infection. US Rotavirus Vaccine Efficacy Group. J Infect Dis 1994;169:900-4.

[4] Velaquez FR, Matson DO, Calva JJ, et al. Rotavirus infection in infants as protection against subsequent infections. New Engl J Med 1996;335(14):1022-8.

[5] Bishop RF, Barnes GL, et al. Clinical immunity after neonatal rotavirus infection. A prospective longitudinal study in young children. N Engl J Med 1983;309:72-6.

[6] Offit. Curr Top Microbiol Immun 1994;85:229.

[7] Coulson BS, Grimwood K, Hudson IL et al. Role of coproantibody in clinical protection of children during reinfection with rotavirus. J Clin Microbiol 1992;30:1678-84.

[8] Matson DO, O'Ryan ML, Herrera I. Fecal antibody responses to symptomatic and asymptomatic rotavirus infections. J Infect Dis 1993;167:577-83.

[9] Velaquez FR, Matson DO, Guerrero ML et al. Serum antibody as a marker of protection against natural rotavirus infection and disease. J Infect Dis 2000;182:1602.

[10] O'ryan ML, Matson DO, Estes MK, Pickering LK. Anti-rotavirus G type specific and isotype-specific antibodies in children with natural infection. J Infect Dis 1994;169:504-11.

[11] Kapikian AZ, Yolken RH, Greenberg HB et al. Gastroenteritis viruses. In: Diagnostic procedures for viral, rickettsial and chlamydial infection, 5th ed. Ed by Lennett H, Schmidt NJ eds, Washington, DC: American Public Health Association 1979; 927-995..

[12] Matson DO, O'Ryan ML, Herrera I, Pickering LK, Estes MK.
Fecal antibody responses to symptomatic and asymptomatic rotavirus infections.
J Infect Dis. 1993 Mar;167(3):577-83.

Appendix M: Supplemental Subject Information and Informed Consent (amended: 3-MAY-2002)

(ONLY FOR STUDY PARTICIPANTS WHO WILL RECEIVE THREE DOSES OF STUDY VACCINE/PLACEBO)

Dear Parent or Guardian:

Your child is part of an investigational rotavirus vaccine study, sponsored by GlaxoSmithKline (GSK) Biologicals (previously known as SmithKline Beecham Biologicals). The results of tests performed on blood samples drawn from infants participating in this study showed that the number of infants who developed antibodies to the vaccine was lower compared to results from studies conducted in Europe. The lower immune response does not mean that your child is not protected against rotavirus gastroenteritis.

A third dose of the HRV vaccine will be therefore administered to 200 subjects among the last infants who joined the study in Brazil or Venezuela in order to find whether an additional dose will result in better response.

If your child is one of 200 infants selected to receive the third dose of the study vaccine, he/she will have 5 study visits. An additional visit will take place two months after the third dose.

One additional blood sample will be taken from your child. No blood sample will be taken from your child at the final visit.

The additional study procedures for your child who will receive the third dose of the study vaccine along with the third dose of the routine vaccines is described below.

Study Participation and Study Procedures

Visit 3 (6 months of age):

- You will be asked to collect a stool sample on the day of vaccination.

- A blood sample (1ml) will be collected.
- Administration of study vaccine/placebo:
  - Oral administration of third dose of the study vaccine/placebo in a subset.
  - Administration of routine vaccines DTPw-HB+Hib vaccine
- Your child will be kept under observation for 30 minutes to check for any immediate vaccine reactions.
- You will be given a diary card at the end of the 30 minutes of observation period to record body temperature (measured by a axillary or rectal route), the number of looser than normal stools passed by the subject, the number of vomiting episodes, any loss of appetite, any fussiness/irritability, any cough/runny nose during the 15-day solicited follow-up period, as well as unsolicited symptoms occurring within 42 days after dose 3.
- You will be asked to collect a stool sample 7 days after vaccination

Your child will have a study visit study (Visit 4) approximately two months after Visit 3. The final study visit (Visit 5) for your child will take place will take place approximately 4 months after.

Visit 4 (8 months of age):

- A physical examination will be carried out.
- A blood sample (3mls) will be collected to test the effectiveness of the investigational vaccine and the routine pediatric vaccines.
- You will continue to record information and to collect stool samples during each episode of gastroenteritis until the final visit at approximately 1 year of age.

Supplemental Consent Statement for subjects receiving three doses of study vaccine or placebo

This vaccine study has been clearly explained to me and I have read and understood the information provided. I agree that my [son/daughter/ward] be enrolled in the study. I understand that I have the right to decline to enter my [son/daughter/ward] in this study and to withdraw from it at any time for any reasons without consequence to his/her present or future health care and attention that he/she receives from his/her healthcare provider. I have been made aware of my right to access and request correction of my child's/ward's personal data. I acknowledge that I have received a copy of this form for future reference.

I, _____ ,
(subject's parent or legal guardian's first name and family name)

hereby freely give my consent for my child/ward to take part in this [clinical/vaccine] study.

Participant's Name: _____
(First Name, Family Name)

Parent/Guardian's name: _____
(First Name, Family Name)

Parent/Guardian's signature: _____

Relationship to participant: _____

Participant's main address: _____

Participant's phone number: _____

Date: _____ **Time:** _____
(DD-MM-YY)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Name of Consent Presenter: _____

Signature of Consent Presenter _____

Appendix N: Supplemental Subject Information and Informed Consent (amended: 20-SEP-2002)

(ONLY FOR STUDY PARTICIPANTS WHO WILL BE FOLLOWED FOR EFFICACY FOR A SECOND YEAR UNTIL 18-24 MONTHS OF AGE)

Dear Parent or Guardian:

Your child is part of an investigational rotavirus vaccine study, sponsored by GlaxoSmithKline (GSK) Biologicals (previously known as SmithKline Beecham Biologicals). The results of tests performed on stool samples collected from infants who developed gastroenteritis (diarrhea) during the study showed that administration of the rotavirus vaccine decreased the number of diarrhea cases. Infants who received the rotavirus vaccine were protected from rotavirus gastroenteritis in comparison to infants who received the placebo (product that looked like vaccine but has no activity).

As your child has not yet completed the follow-up visit at approximately one year of age, we propose to follow him/her for a second year (until age 18-24 months). About 1000 children are expected to participate in the second year follow-up. (amended: 26 March 2003).

Your child will have an additional study visit at approximately 18-24 months old. No additional blood samples will be taken from your child.

The additional study procedures for your child who will be followed for the second year are described below.

Study Participation and Study Procedures

Interval between visit at 1 year old and visit at approximately ~~2 years~~ 18 – 24 months old (amended: 26 March 2003)

You will continue the efficacy follow-up during the interval between follow-up visit at one year of age and follow-up visit at 18-24 months ~~two years~~ of age. (amended: 26 March 2003)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

- For each episode of gastroenteritis, you will be instructed to contact the study site personnel and to daily record the following on a diary card until symptoms resolve: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. You will be asked to collect one stool sample. A second stool sample will be collected on a different day if the first sample was insufficient. We will diagnose rotavirus gastroenteritis by collecting stool samples from infants that develop gastroenteritis (diarrhea). We will test the stool samples for rotavirus ~~and some other pathogens~~. (amended: 26 March 2003)

Follow-up visit at maximum 24 of age (Brazil and Venezuela: *until 01-> 31 October 2003*) (Mexico: June 1-> 30, 2003 after the end of RV season) (amended: 26 March 2003) (amended: 21 August 2003)

- A physical examination will be carried out.
- The investigator will collect the completed diary card from you.
- Your child's/ward's participation in the study will be completed.

- **Supplemental Consent Statement for subjects who will be followed for efficacy for a second year *until 18-24 months* of age**

This vaccine study has been clearly explained to me and I have read and understood the information provided. I agree that my [son/daughter/ward] be enrolled in the study. I understand that I have the right to decline to enter my [son/daughter/ward] in this study and to withdraw from it at any time for any reasons without consequence to his/her present or future health care and attention that he/she receives from his/her healthcare provider. I have been made aware of my right to access and request correction of my child's/ward's personal data. I acknowledge that I have received a copy of this form for future reference.

I, _____ **,**
(subject's parent or legal guardian's first name and family name)

hereby freely give my consent for my child/ward to take part in this [clinical/vaccine] study.

Participant's Name: _____
(First Name, Family Name)

Parent/Guardian's name: _____
(First Name, Family Name)

Parent/Guardian's signature: _____

Relationship to participant: _____

Participant's main address: _____

Participant's phone number: _____

Date: _____ **Time:** _____
(DD-MM-YY)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Name of Consent Presenter: _____

Signature of Consent Presenter _____

Appendix K: Protocol Amendments/Modifications

Amendment 1

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Rationale of the amendment:

The target concentration of one of the clinical lots to be used in this clinical study is $10^{6.1}$ ffu. The actual release titer of the lot DRVC004A46 to be used in the proposed trial is $10^{5.8.}$ ffu. The variability of the titration test which is performed for routine vaccine lot release is 0.3 logs. The clinical lot $10^{5.8}$ ffu is in the range of the targeted dose. The following changes were also implemented: to direct parents to contact study personnel for every case of gastroenteritis, to define the immunogenicity and stool subset, delete gastroenteritis stool testing for cryptosporidia; and to clarify the use of several lots for the commercial vaccines.

The following strikethrough and bolded italic text were amended:

Throughout the protocol including Study Title, Synopsis, Section 1.2 – Rationale, Section 2, Section 3 – Study design, Section 6.1.1 – SmithKline Beecham Biologicals' HRV vaccine, Appendix H, all references to viral concentration $10^{6.1}$ ffu were changed to $10^{5.8}$ ffu.

Cover Page

SmithKline Beecham *Mexico*
Av. Insurgentes Sur 1605 piso 20
Colonia San Jose Insurgentes
Mexico D.F.CP04800

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

SmithKline Beecham *Colombia*
Avenida El Dorado No 91 - 50
Bogota, Colombia

Medical Monitor (Venezuela)

[redacted] MD
SmithKline Beecham Costa Rica
300 m Este de la Escuela La Betania
Carretera Sabanilla
Apdo 10196 – 1000
San Jose, Costa Rica
Tel: [redacted]
Fax: [redacted]

SYNOPSIS

Rationale

The main objective of this study is to evaluate the efficacy of the study vaccine to prevent any rotavirus gastroenteritis. This study will also contribute to dose selection ***and assess the immune response to concomitantly administered routine vaccinations (DTPw-HB+Hib vaccine*).**

Objectives

Primary

- For ***a range of*** viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' HRV vaccine, to demonstrate the efficacy of two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations in preventing any rotavirus gastroenteritis* during the period starting from 2 weeks after dose 2 until the end of the efficacy follow-up period.

Secondary

Efficacy

- For ***a range of*** viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$

ffu) of SB Biologicals' HRV vaccine, to assess if two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations can:

- ***Prevent rotavirus gastroenteritis due to virus types heterologous to vaccine strain.***

Immunogenicity

- To assess vaccine take, in subjects previously uninfected with rotavirus before vaccination, two months after each study vaccine dose ***in a subset of*** 800 subjects ~~enrolled~~.
- To explore ***in a subset of*** 800 subjects the effect of SB Biologicals' rotavirus vaccine on the immune response to concurrently administered routine vaccinations.
- To assess viral shedding in the vaccine groups ***in a subset***.

Note: the immunogenicity/stool subset is described in section 6.4.

Study design

Study Procedures

Visit 2 (4 Months of Age) – Blood sample in a subset (~~the first~~ 800 subjects ~~enrolled~~), Dose 2 of study vaccine or placebo and Dose 2 of routine vaccinations (DTPw-HB+Hib vaccine).

Visit 3 (6 Months of Age) – Blood sample in a subset (~~the first~~ 800 subjects ~~enrolled~~) and Dose 3 of routine vaccinations (DTPw-HB+Hib vaccine).

- Stool samples will be collected from ~~the first~~ ***a subset of*** 400 subjects enrolled on the day of administration of dose 1 and dose 2 and on day 7 following each dose of study vaccine.
- For each suspected gastroenteritis episode occurring from day of dose 1 until study end, ***a stool sample will be collected*** as soon as possible after the onset of gastroenteritis ***and will be brought as soon as possible to the study site.*** A second stool specimen will be collected ~~by the Health Worker~~ if the first stool sample was not sufficient.

Secondary endpoints

Efficacy

- ***Occurrence of rotavirus gastroenteritis due to virus types heterologous to vaccine strain during the period starting from two weeks after dose 2 until the end of the efficacy follow-up period.***

Immunogenicity endpoints

Two months after dose 2 (at Visit 3) and at year 1 (at Visit 4) in a subset (~~the first~~ 800 subjects ~~enrolled~~).

Analyses

The final analysis will be performed at the end of the efficacy follow-up period, after all enrolled subjects have completed visit 4. An interim analysis will be performed on immunogenicity and reactogenicity of the vaccines ***to provide early information on dose selection of phase III studies.*** The interim results will be limited to summaries by group.

2.1 Primary objective

- For ***a range of*** viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{\mathbf{5.8}}$ ffu) of SB Biologicals' HRV vaccine, to demonstrate the efficacy of two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations in preventing any-rotavirus gastroenteritis* during the period starting from 2 weeks after dose 2 until the end of the efficacy follow-up period.

2.2 Secondary objectives

Efficacy

For ***a range of*** viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{\mathbf{5.8}}$ ffu) of SB Biologicals' HRV vaccine, to assess if two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations can:

- ***Prevent rotavirus gastroenteritis due to virus types heterologous to vaccine strain.***

Immunogenicity

- To assess vaccine take, in subjects previously uninfected with rotavirus before vaccination, two months after each study vaccine dose ***in a subset of*** 800 subjects ~~enrolled~~…
- To explore ***in a subset of*** 800 subjects the effect of SB Biologicals' rotavirus vaccine on the immune response to concurrently administered routine vaccinations.
- To assess viral shedding in the vaccine groups ***in a subset***.

Note: the immunogenicity/stool subset is described in section 6.4.

3. Study Design Overview

Visit 2 (4 Months of Age) – Blood sample in a subset (~~the first~~ 800 subjects ~~enrolled~~), Dose 2 of study vaccine or placebo and Dose 2 of routine vaccinations (DTPw-HB+Hib vaccine).

Visit 3 (6 Months of Age) – Blood sample in a subset (~~the first~~ 800 subjects ~~enrolled~~) and Dose 3 of routine vaccinations (DTPw-HB+Hib vaccine).

An interim analysis will be performed on immunogenicity and reactogenicity of the vaccines ***to provide early information on dose selection of phase III studies.***

- Stool samples will be collected from ~~the first~~ ***a subset of*** 400 subjects enrolled on the day of administration of dose 1 and dose 2 and on day 7 following each dose of study vaccine.

- For each suspected gastroenteritis episode occurring from day of dose 1 until study end, ***a stool sample will be collected*** as soon as possible after the onset of gastroenteritis ***and will be brought as soon as possible to the study site.*** A second stool specimen will be collected ~~by the Health Worker~~ if the first stool sample was not sufficient.

4.3 Exclusion criteria

- Acute disease at time of enrollment. (Acute disease is defined as the presence of moderate or severe illness with ***or without*** fever i.e. temperature ≥ 37.5°C as measured by an axillary thermometer or ≥ 38.0°C as measured by a rectal thermometer). A temperature greater than or equal to these cut-off warrants deferral of the vaccination pending recovery of the subject.

5.2 General study aspects

Each study site will receive a "Road book" providing guidelines for the conduct of the study.

Surveillance of gastroenteritis and collection of stool samples

An active surveillance for gastroenteritis ~~efficacy~~ will be conducted via weekly visits to a subject by study personnel (Health Worker) starting 1 week after dose 1 and ending at Visit 4. There ***need*** be no weekly follow-up in weeks when a study clinic visit is scheduled. ~~For each subject, assuming enrollment at 8 weeks of age and completion at 52 weeks of age, there will be 41 weekly home visits.~~ The weekly follow-up by a Health Worker may be done at the subject's home, at a health clinic, or other mutually convenient place. At weekly follow-up, Health Workers will inquire about the occurrence of gastroenteritis and serious adverse events (disabling illness, hospitalization, death). In cases of gastroenteritis, ***parents should contact the study site personnel***…

~~Subjects enrolled in this study will be followed from the day of first vaccination until 1 year of age for the occurrence of gastroenteritis. For each gastroenteritis episode, 1 stool sample should be collected. A second stool sample will be collected on a different day if the first stool sample was insufficient.~~

Parents/guardians should use the containers… The parents/guardians/***health worker*** should write the date of collection on the container/ziplock bag label with a black ink or ballpoint pen.

5.3 Outline of study procedures

Age	**2 months**	**4 months**	**6 months**	**1 year**
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2** ***MO 4***	**Post vacc 2** **MO *10***
Randomisation	•			
Recording of ***solicited symptoms,*** non serious adverse events within 42 days after dose 1 and dose 2, by investigator		•	•	
Contact (field visit) every week ~~to check on the occurrence of any serious AE or gastroenteritis episodes~~	◊	◊	◊	◊
Return of ***GE*** diary ~~cards~~	•	•	•	•
GE diary ~~card~~ transcription		•	•	•

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

~~The double-line border following Visit 3 aims to distinguish the data that will be included in the analyses of immunogenicity/safety on all available data around June 30, 2001~~.

5.4 Detailed description of study stages/visits

Visit 1: Dose 1	6 to 12 weeks (42 to 90 days) of age

- ***Randomisation (or subject) number attribution.***
- Collection of a stool sample at the day of or 1 day prior to vaccination from ~~the first~~ ***a subset of*** 400 subjects enrolled, to determine the presence of rotavirus.

Interval between Visit 1 and 2

Day 0 to Day 14 (At bedtime):

- The following data will be recorded ~~by the parent/guardian~~ on the diary-card:

Day 7 ± 1:

- ***Collection of a stool sample in a subset (400 subjects).***

Any time between Visit 1 and Visit 2

- Recording ~~by the parent/guardian~~ of unsolicited symptoms, including any SAE.
- Diary cards will also be provided to the parents/guardians of all subjects to daily record the following information until symptoms resolve during each suspected episode of gastroenteritis occurring between visits: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. ~~Parent/guardians will be asked to record whether~~ ***R***ehydration or other medication ***will be recorded***.

Visit 2: Vaccine dose 2	4 Months of Age (49 to 83 days after 1st vaccination)

- Collection of blood sample in a subset (~~first~~ 800 subjects ~~enrolled at Visit 1~~) for serology: a minimum of 1 ml of whole blood to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.
- Collection of a stool sample at the day of or 1 day prior to vaccination from a subset (~~first~~ 400 subjects ~~enrolled at Visit 1~~) to determine the presence of rotavirus.

Interval between Visit 2 and 3

Day 0 to Day 14 (At bedtime):

- The following data will be recorded ~~by the parent/guardian~~ on the diary card:

Day 7 ± 1:

- ***Collection of a stool sample in a subset (400 subjects).***

Any time between Visit 2 and Visit 3

- Recording ~~by the parent/guardian~~ of unsolicited symptoms, including any SAE.

- Diary cards will also be provided to the parents/guardians of all subjects to daily record the following information until symptoms resolve during each suspected episode of gastroenteritis occurring between visits: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. ~~Parent/guardians will be asked to record whether~~ ***R***ehydration or other medication ***will be recorded***.

Visit 3: Dose 3 of routine vaccines and Follow-up	**6 Months of Age (49 to 83 days after 2nd vaccination)**

- Collection of blood sample in a subset (~~first~~ 800 subjects ~~enrolled at Visit 1~~) for serology: a minimum of 3 mls of whole blood to provide a minimum of 1.5 mls of serum according to instructions in Appendix D.

Interval between Visit 3 and Visit 4

Continued efficacy follow-up:

- A Health Worker will visit the parent/guardian weekly (except for weeks when a study clinic visit is scheduled) to assess the completion or collection of diary card information, check on the occurrence of ~~any adverse event, including any~~ SAE or gastroenteritis episodes and if appropriate, collect stool samples.
- Diary cards will also be provided to the parents/guardians of all subjects to daily record the following information until symptoms resolve during each suspected episode of gastroenteritis occurring between visits: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. ~~Parent/guardians will be asked to record whether~~ ***R***ehydration or other medication ***will be recorded***.

Visit 4: Efficacy Follow-up	**1 Year of Age (160 - 200 days after Visit 3)**

- Collection of blood sample from subjects for serology: a minimum of 3 mls of whole blood for the subjects in the subset (~~first~~ 800 subjects ~~enrolled at Visit 1~~) and a minimum of 1 ml in all other subjects.
- Document the administration of routine EPI vaccines ***in the interval before Visit 4; there is no requirement to document vaccines administered at Visit 4***.

5.5.2 Laboratory assays

Stool Analysis

Stool samples will be collected from ~~the first~~ ***a subset of*** 400 subjects enrolled, on the day of or 1 day prior to administration of dose 1 and dose 2 and on day 7 following each dose… If rotavirus is detected (by rapid rotavirus detection kit) in the stool sample, part of the stool sample should be analysed locally for culture of enteric pathogens ~~including~~ ***such as*** Salmonella, Shigella, and Campylobacter. ETEC and ***EPEC*** ~~cryptosporidiosis~~ will be determined ~~by PCR~~ at a central laboratory. The other part of the stool sample will be sent to core laboratory ***A*** to be tested by ELISA to confirm the presence of rotavirus. The other part of the stool sample will be sent to core laboratory***(ies)*** ~~B~~ to be tested by ELISA to confirm the presence of rotavirus. ***Diagnosis of rotavirus gastroenteritis will be by ELISA***…

Any additional testing on stools will be performed if deemed necessary by SmithKline Beecham Biologicals if any findings in the present study or in other studies necessitate investigation of the immunogenicity of the vaccine.

Immunogenicity

For the ***immunogenicity subset (N=800)*** ~~first 800 subjects enrolled~~, a minimum of 1 ml of whole blood will be collected at Visits 1 and 2 and a minimum of 3 mls of whole blood will be collected at Visits 3 and 4, using tubes with serum separator.

Antigen	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off	Core Laboratory
rotavirus	ELISA	in-house	U/ml	20	**TBD***
anti-PRP	ELISA	in-house	mcg/ml	0.15	***TBD***
anti-D	ELISA	in-house	IU/ml	0.1	***TBD***
anti-T	ELISA	in-house	IU/ml	0.1	***TBD***
anti-BPT	ELISA	in-house	EL.U/ml	15	***TBD***
anti-HBs	ELISA	in-house	mcg/ml	10	***TBD***

Antigen	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off	Core Laboratory
anti-polio 1	micro-neutralization test	in-house	-	8	***TBD***
anti-polio 2	micro-neutralization test	in-house	-	8	***TBD***
anti-polio 3	micro-neutralization test	in-house	-	8	***TBD***

5.5.3 Serology plan

Study Group	Blood sampling timepoint			Antigen	No. subjects
	Timing	**Month**	**Visit no.**		
A, B & C	Pre	0	1	rotavirus only	2640
A, B & C	Post I	2	2	rotavirus only	800
A, B & C	Post II ***MO 4***	4	3	all	800
A, B, C & D	Post II MO ***10***	10	4	all rotavirus only	800 1840

6.1.4 Commercial EPI vaccines

Vaccine	Lot no.	Formulation One dose (0.5ml) of vaccine contains	Presentation
DTPw-HB+Hib vaccine	~~One~~ Commercial ***Lots*** will be used	Each 0.5 mL dose contains: Whole cell pertussis ≥ 4 IU Diphtheria toxoid ≥ 30 IU (25 Lf); Tetanus toxoid ≥ 60 IU (10 Lf); HBsAg 10 mcg; PRP 10 mcg bound to 30 mcg tetanus toxoid; 2-phenoxyethanol, polysorbate 20, Sodium chloride, thiomersal, lactose, water for injection	DTPw-HB+Hib vaccine is presented as 2 individual components. DTPw-HB vaccine ~~as a turbid white suspension in a monodose vial~~ and Hib vaccine ~~as a white pellet in a glass vial.~~

Vaccine	Lot no.	Formulation One dose (0.5ml) of vaccine contains	Presentation
Polio Sabin	~~One~~ Commercial ***Lots*** will be used	Poliovirus type 1 (LS-c, 2ab) 10^6 $TCID_{50}$; Poliovirus type 2 (P712, Ch, 2ab) 10^5 $TCID_{50}$; Poliovirus type 3 (Leon $12a_1b$) $10^{5.5}$ $TCID_{50}$; Magnesium chloride; Neomycin	Liquid~~: multi-dose vials Ready for use.~~

6.4 Treatment allocation and randomisation

Randomisation of supplies

To allow SmithKline Beecham to take advantage of greater rates of recruitment than anticipated at individual centres in this multicentre study, and to thus reduce the overall study recruitment period, a 10% over-randomisation of supplies will be prepared~~ to provide 2904 vaccine numbers~~.

Randomisation of subjects

The randomisation will be performed using a central randomisation system on Internet. The randomisation algorithm uses a minimisation procedure stratified by centre [23]. ***All countries/centers must use internet randomization, however in case of unexpected technical problems, the classical randomization will be done.***

For centres using the Internet randomisation, **w**hen a subject is eligible and the parent/guardian has given informed consent, the person who is in charge of the vaccination will access the randomisation system on Internet. Upon providing the subject initials and birth date, the randomisation system will determine the vaccine number to be used for the subject. ***For centres using the classical randomisation, subjects will be administered the vaccine dose with the lowest number still available at the study centre.*** The vaccine number will also be used as patient identification number (PID) for all data collected on the subject under the study.

The first 200 (100) subjects enrolled in each country will provide a blood (stool) sample. The remaining subset of 200 (100) blood (stool) samples will come indifferently from any of the participating countries, according to the order of enrollment. In all, the subset that provides additional blood samples will contain 800 subjects and the subset that provides stool samples on day 0 and day 7 will contain 400 subjects.

8.1 Eliciting and documenting adverse events

Recording adverse events

In case a subject is diagnosed with intussusception immediate reporting to the sponsor will be mandatory. Refer to section 8.5. The diagnosis of intussusception should be documented ***by*** radiography…

8.5.2 Reporting serious adverse events

Study Contact for Reporting Serious Adverse Events	
Brazil *Medical Monitor:* [redacted] [redacted] MD **(amended: 26 March 2003)** Tel: [redacted] ***Cell:*** [redacted]	*Clinical Research Associate:* [redacted] Tel: [redacted] *Clinical Research Associate:* [redacted] CP04800 Tel: [redacted] Cell: [redacted]
Venezuela *Medical Monitor:* [redacted] MD SmithKline Beecham ***Costa Rica*** ***300 m Este de la Escuela La Betania*** ***Carretera Sabanilla*** ***Apdo 10196 – 1000*** ***San Jose, Costa Rica*** Tel: [redacted] Fax: [redacted]	*Clinical Research Associate:* [redacted] SmithKline Beecham, ***Colombia*** *Avenida El Dorado No 91 - 50* ***Bogota, Colombia*** Tel: [redacted] Fax: [redacted]
Back-up Study Contact for Reporting Serious Adverse Events	
Venezuela: [redacted] ***SmithKline Beecham Venezuela*** ***Calle La Guarita, Edificio Los Frailes, Piso 3, Chuao, Caracas*** ***Tel:*** [redacted] ***Fax:*** [redacted]	

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

10.2 Secondary endpoints

Efficacy endpoints

- ***Occurrence of rotavirus gastroenteritis due to virus types heterologous to vaccine strain during the period starting from two weeks after dose 2 until the end of the efficacy follow-up period.***

Immunogenicity endpoints

Two months after dose 2 (at Visit 3) and at year 1 (at Visit 4) in a subset (~~the first~~ 800 subjects ~~enrolled~~).

10.3 Study cohorts/data sets to be evaluated

ATP cohort for analysis of immunogenicity

For inclusion in the ATP cohort for immunogenicity, intervals between visits 1 and 2 and between visits 2 and 3 need to be at least 49 days and must not exceed 83 days.

10.4 Estimated sample size

The primary objective is to demonstrate that, for ***a range of*** viral concentration ($10^{4.7}$-ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' HRV vaccine, two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations can prevent rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the efficacy follow-up period following vaccination.

The analysis will consist in looking at the pooled vaccine groups versus placebo and each vaccine group versus placebo.

In order to control the risk of falsely concluding below 5%, the primary objective will be addressed using a hierarchical testing. ***Pooled vaccine groups will be first tested and, only if efficacy has been demonstrated, will t***he vaccine with a viral concentration of $10^{5.8}$ ffu ***be tested***. ***Likewise, only if efficacy of vaccine with a***

viral concentration of $10^{5.8}$ ffu has been demonstrated, will the vaccine with a viral concentration of $10^{5.2}$ ffu be tested...

The target sample size is 2640 enrolled subjects to reach 2360 subjects in the ATP cohort of efficacy (590 in each group). Table 10.4.1 indicates the level of accuracy that can be expected for the evaluation of efficacy ***for a vaccine group*** to any rotavirus gastroenteritis (primary objective) and to severe rotavirus gastroenteritis (secondary objective) with this sample size. ***Power is higher for the evaluation of efficacy on pooled vaccine groups.***

10.5 Final analyses

The final analysis will be performed at the end of the efficacy follow-up period, after all enrolled subjects have completed visit 4. An interim analysis will be performed on immunogenicity and reactogenicity of the vaccines ***to provide early information on dose selection.*** The interim results will be limited to summaries by group.

10.5.4 Efficacy analysis

The vaccine efficacy rate (VE), expressed as 100% X (1-Relative Risk), will be calculated ***for pooled vaccine groups and for each vaccine group,*** with their 95% CI (see Appendix J for mathematical detail) against:

- ***rotavirus gastroenteritis due to virus types heterologous to vaccine strain.***

The primary objective is to demonstrate that ***pooled HRV vaccine groups can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the efficacy follow-up period, and subsequently that*** the HRV vaccine with a viral concentration of $10^{5.8}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the efficacy follow-up period, and subsequently that the HRV vaccine with a viral concentration of $10^{5.2}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the efficacy follow-up period, and subsequently that the HRV vaccine with a viral concentration of $10^{4.7}$ ffu can prevent rotavirus gastroenteritis

occurring from two weeks after dose 2 until the end of the efficacy follow-up period.

The efficacy of the pooled vaccine groups will be first evaluated. If the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the efficacy follow-up period following vaccination in the pooled HRV groups is statistically significantly lower than in the placebo group (two-sided Fisher Exact test : $p < 0.05$), one will conclude that the efficacy of the pooled HRV vaccine groups in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the efficacy follow-up period has been demonstrated.

If in addition the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the efficacy follow-up period following vaccination in the HRV group with a viral concentration of $10^{5.8}$ ffu is statistically significantly lower than in the placebo group (two-sided Fisher Exact test : $p < 0.05$), one will conclude that the efficacy of the HRV vaccine with a viral concentration of $10^{5.8}$ ffu in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the efficacy follow-up period has also been demonstrated.

And, if in addition the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2…

10.6 Interim analysis

An interim analysis will be performed ***to provide early information on dose selection***…

Appendix C: Overview of the recruitment plan

- Target enrollment will be 2640 subjects (approximately ***1020 in Brazil***; 800 in Mexico and 820 in Venezuela).

- ~~Enrollment will start around January 15, 2001.~~

Appendix D: Handling of Biological Samples Collected by the Investigator

4. Sorting and storage

The tubes of serum should be stored in a vertical position at a temperature between -20°C and -70°C until shipment to core laborato***y*** (ies) ~~A and/or B~~. Wherever possible, a backup facility for storage of serum samples should be available.

Instructions for Handling of Stool Samples

The stool specimens will be processed by the investigator's laboratory into stool suspensions and then stored at a temperature between -20°C and -70°C until shipment to core laboratory***(ies)*** ~~B~~.

Appendix E: Shipment of Biological Samples

The investigator will coordinate the shipment of samples to ~~core laboratory B (SB Biologicals in Rixensart, Belgium or to Dr.~~ [redacted] ~~laboratory in Cincinnati, OH.) and/or~~ a core laboratory to be determined.

Appendix F: Laboratory Assays

1.2.2 *Antigen Detection in GE Stool Samples*

A rapid screening will be performed at the study sites to determine the presence of rotavirus in the stool using a commercial test (Rotaclone or equivalent). Additional testing for other pathogens is done on rotavirus positive GE stool samples, as described in section 5.5.2.

Appendix H: Sample Subject Information and Informed Consent

2. Description/Purpose of the Study

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

This is a medical research study... We will look for side effects (like fever, ***loss of appetite*****,** fussiness/***irritability***, vomiting, diarrhea ***[three or more looser than normal stools within a day]*** and runny nose/cough).

We will test the human rotavirus vaccine at 3 different strengths. Various strengths of the investigational rotavirus vaccine have been tested already in ***more than*** 200 infants and previously an earlier version of the vaccine made by another manufacturer was tested in approximately 200 infants.

After your child is vaccinated, we will see whether the human rotavirus vaccine prevents any and severe rotavirus gastroenteritis. We will diagnose rotavirus gastroenteritis by collecting stool samples from infants that develop gastroenteritis (diarrhea). We will test the stool samples for rotavirus ***and some other pathogens.***

4. Study Participation and Study Procedures

Also at that appointment, study personnel will ask you questions about your child's medical history and medicines that your child may be taking. For ~~the first~~ ***a subset of*** 400 subjects enrolled, we will collect a stool sample on the day of vaccination. We will collect a stool sample on the day of vaccination…

Visit 1 (2 months of age):

- You will be asked questions about your child's health, your child will be examined by the doctor and his/her temperature will be taken. You will be asked to provide a stool sample ***if your child is one of 400 infants selected for stool tests. This stool sample will be tested for rotavirus.***
- Randomisation will be performed after the blood draw.
- If your child ***is*** one of 400 ***infants selected for stool tests***, you will be asked to collect a stool sample 7 days after vaccination.
- For each episode of gastroenteritis, ***you*** will be instructed ***to contact the study site personnel and*** to daily record the following on a diary card until symptoms resolve: axillary/rectal temperature, number of vomiting episodes,

and number of looser than normal stools passed by the subject. You will be asked to collect one stool sample. A second stool sample will be collected ~~by the Health Worker~~ on a different day if the first sample was insufficient.

Visit 2 (4 months of age):

- If your child ***is*** one of 400 ***infants selected for stool tests***, you will be asked to collect a stool sample on the day of vaccination.
- If your child is ***one of*** 800 ***infants selected for blood tests of the vaccine***, a blood sample (1ml) will be collected ~~from your child to test the effectiveness of the vaccine~~.
- If your child ***is*** one of 400 ***infants selected for stool tests***, you will be asked to collect a stool sample 7 days after vaccination.
- For each episode of gastroenteritis, ***you*** will be instructed ***to contact the study site personnel and*** to daily record the following on a diary card until symptoms resolve: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. You will be asked to collect one stool sample. Second stool sample will be collected ~~by the Health Worker~~ on a different day if the first sample was insufficient.

Visit 3 (6 months of age):

- If your child is ***one of*** 800 ***infants selected for blood tests*** a blood sample (3mls) will be collected ~~from your child~~ to test the effectiveness of the investigational vaccine and the routine pediatric vaccines.
- For each episode of gastroenteritis, ***you*** will be instructed ***to contact the study site personnel and*** to daily record the following on a diary card until symptoms resolve: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. You will be asked to collect one stool sample. A second stool sample will be collected ~~by the Health Worker on a different day~~ if the first sample was insufficient.

Visit 4 (1 year of age):

- If your child is ***one of*** 800 ***infants selected for blood tests***, a blood sample (3mls) will be collected ~~from your child~~ to test the effectiveness of the investigational vaccine and the routine pediatric vaccines. For all other children, a 1 ml blood sample will be taken from your child to determine the effectiveness of the ***investigational*** vaccine ***only***.
- ~~For each episode of gastroenteritis, parents/guardians will be instructed to daily record the following on a diary card until symptoms resolve: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. You will be asked to collect one stool sample. A second stool sample will be collected by the Health Worker on a different day if the first sample was insufficient.~~

The quantity of the stool sample should be at minimum 2 spoons (the spoon is within the stool container) and at maximum half of the container. Write the name, date of collection on the container label with a black ballpoint pen ~~and store the container in the freezer, screw cap facing upwards~~. A field worker will collect the stool samples.

4. Potential Risks Associated with the Study

There are risks if your child enters this study. The risks come from the use of an investigational human rotavirus vaccine and from collection of ***a maximum of 4*** blood samples. These risks are explained below.

The human rotavirus vaccine may cause allergic reactions… Your child must stay in your doctor's office for 30 minutes after each ***study*** vaccine dose so that any reaction can be treated.

The human rotavirus vaccine given to your child… ***If your child is one of 800 infants selected for blood tests***, we will test your child's blood for antibody levels expected from the routine vaccines at 6 and 12 months of age…

If your child is ***one of 800 infants selected for blood tests***, a 1 ml blood sample will be taken at Visits 1 and 2 and a 3 ml blood sample will be taken at Visits 3 and 4…

Your child will receive routine vaccinations recommended by the EPI. These vaccines may cause side effects including pain and swelling at the injection site, high fever, fussiness/irritability, vomiting, and poor feeding***, and in very rare cases allergic reactions.***

Appendix I: Follow-up of intussusception cases

2. Data collection for intussusception cases

The investigator will document all available information regarding any intussusception cases occurring during the clinical studies on the Serious Adverse Event pages ~~contained in the individual eCRF~~ and fax within 24 hours (1 calendar day) of his/her becoming aware of the event to the SmithKline Beecham Contact for Serious Adverse Event (SAE) Reporting.

To allow for a complete assessment of the intussusception cases, information on the subject's feeding practices, immunization history, as well as any other information thought necessary for assessment by the study staff should be reported to the SB safety contact ***by using the IS reporting form***.

3. Serum, throat and stool specimen collection from intussusception cases

If possible a stool specimen should be collected… The hospital microbiology laboratory should divide each stool specimen into an aliquot for its own testing and two additional aliquots of at least 2 grams each to be frozen at ***–20°C to*** –70°C... One swab specimen should be submitted for bacterial culture and the other 2 swabs should be placed each in a separate tube of 2 ml of sterile virus transport media and frozen at ***–20°C to*** –70°C.

A throat swab should be collected as soon as possible after intussusception is diagnosed. The throat swab should be placed in 2 ml of sterile virus transport media and frozen at ***–20°C to*** –70°C.

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. **(amended: 12-FEB-2001)**

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Approved by:

Director

[redacted] dd-mm-yy

Group Director

[redacted] dd-mm-yy

Head Biometrican

[redacted] dd-mm-yy

Investigators

Dr. [redacted] dd-mm-yy

Dr. [redacted] dd-mm-yy

Dra. [redacted] dd-mm-yy

Dra. [redacted] dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Modification 1

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Rationale of the modification:

This protocol was modified to change the principal investigator and medical monitor in Venezuela, to delete a principal investigator in Brazil, to change the clinical research associate in Brazil and to delete [redacted] as the back-up contact for reporting serious adverse events.

The following strikethrough and bolded italic text were amended:

Cover Page

(Principal) Investigators	~~Dra.~~ [redacted] ~~Brasil~~ [redacted]
Medical Monitor (Venezuela)	***Dr.*** [redacted] SmithKline Beecham ***Venezuela*** ***Calle La Guarita Edf. Los Frailes. Piso 3*** ***Chuao / Caracas*** ***Venezuela*** Tel: [redacted] ***Mobile:*** [redacted]

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

(Principal) Investigator ***Dra.*** [redacted] ***M.D.***
[redacted]
Venezuela

8.5.2 Reporting serious adverse events

Study Contact for Reporting Serious Adverse Events	
Brazil Venezuela *Medical Monitor:* ***Dr.*** [redacted] SmithKline Beecham ***Venezuela*** ***Calle La Guarita Edf. Los Frailes.*** ***Piso 3*** ***Chuao / Caracas*** ***Venezuela*** Tel: [redacted] ***Mobile*:** [redacted]	*Clinical Research Associate:* [redacted] SmithKline Beecham Brazil, Av. Comandante Guaranys, 447 Jacarepagua, Rio de Janeiro Brazil 22775-610 Tel: [redacted] or [redacted] Fax: [redacted]
Back-up Study Contact for Reporting Serious Adverse Events	
~~Venezuela:~~ [redacted] ~~SmithKline Beecham Venezuela~~ ~~Calle La Guarita, Edificio Los Frailes, Piso 3, Chuao, Caracas~~	

~~Tel:~~ [redacted]
~~Fax:~~ [redacted]

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	**May 14, 2001**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by:
Clinical Development Manager

[redacted] dd-mm-yy

Investigators

Dr. [redacted] dd-mm-yy

Dr. [redacted] dd-mm-yy

Dra. [redacted] dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Site-specific Amendment

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.
Date	October 10, 2001 – Site-specific amendment

Rationale of the amendment:

Natural rotavirus infection is known to afford clinical protection against subsequent episodes of disease and specific IgA in serum and in fecal samples are considered to be good predictors of protection against natural rotavirus illness.

Fecal rotavirus IgA immune response and the role of IgA antibodies as marker of protection against rotavirus disease will be therefore evaluated in a site-specific study in Venezuela. A subset of 200 infants from Venezuela enrolled in study rota-006 and receiving GSK Biologicals' HRV vaccine or placebo will participate in this site-specific study.

The following bolded italic text were amended:

Synopsis

Study design

Study Procedures

- ***As part of a site-specific sub-study in Venezuela, stool samples, up to a maximum of 10 over the study period, will be collected from a subset of 200 subjects enrolled in Venezuela. Also, two additional stool samples will be collected from this subset during each gastroenteritis episode occurring during***

the study period.

3. Study Design Overview

- ***As part of a site-specific sub-study in Venezuela, stool samples, up to a maximum of 10 over the study period, will be collected from a subset of 200 subjects enrolled in Venezuela. Also, two additional stool samples will be collected from this subset during each gastroenteritis episode occurring during the study period.***

5.4 Detailed description of study stages/visits

Please refer to Appendix L for information on additional stool sampling for the subset of 200 subjects participating in the site-specific study in Venezuela.

5.5.2 Laboratory assays

Stool Analysis

Please refer to Appendix L for information on laboratory assays to be performed on additional stool samples collected from the subset of 200 subjects participating in the site-specific study in Venezuela.

10.5.3 Analysis of immunogenicity

Please refer to Appendix L for information on analysis and reporting of results on stool analysis from the subset of 200 subjects participating in the site-specific study in Venezuela.

Appendix H: Sample Subject Information and Informed Consent

4. Study Participation and Study Procedures

If you live in Venezuela, you may be asked to collect 10 additional stool samples from your child for further testing of your child's response to the vaccine. This additional testing will be performed in 200 infants.

Visit 1 (2 months of age):

- ***If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect a stool sample just before vaccination and 14 and 28 days after vaccination. This stool sample will be used for further testing of your child's response to the vaccine.***

- ***If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect two additional stool samples for each episode of gastroenteritis: one at 1-5 days after onset of symptoms and the second at 14 days after onset of symptoms.***

Visit 2 (4 months of age):

- ***If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect a stool sample just before vaccination and 14 and 28 days after vaccination. This stool sample will be used for further testing of your child's response to the vaccine.***

- ***If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect two additional stool samples for each episode of gastroenteritis: one at 1-5 days after onset of symptoms and the second at 14 days after onset of symptoms.***

Visit 3 (6 months of age):

- ***If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect a stool sample every two months from six months of age until Visit 4.***

- ***If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect two additional stool samples for each episode of***

gastroenteritis: one at 1-5 days after onset of symptoms and the second at 14 days after onset of symptoms.

Appendix L: Site-specific study of rotavirus specific IgA antibodies in feces in Venezuela

Appendix L, with details regarding the site-specific study in Venezuela, was added to the protocol.

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by:

Director

[redacted] dd-mm-yy

Head Biometrican

[redacted] dd-mm-yy

Investigator

Dra. [redacted] dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Amendment 2

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Rationale of the amendment:

This amendment will allow termination of enrolment in Mexico by end December 2001 to avoid vaccinating subjects during the rotavirus season. Indeed, rotavirus infection either prior to vaccination or during the vaccination period is an elimination criterion from the primary efficacy analysis and if enrolment was continued during the season, a large proportion of infants enrolled during this period would then have to be eliminated. On the other hand, there is no rotavirus season as such in Venezuela and Brazil and enrolment of eligible subjects will continue in these two countries with the aim to compensate the lower recruitment in Mexico.

The addresses of the GSK offices in Brazil and Mexico have been modified.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

The following strikethrough and bolded italic text were amended:

Cover Page
~~Av. Comandante Guaranys, 447~~
~~Jacarepagua, Rio de Janeiro~~
~~Brasil 22775-610~~
GlaxoSmithKline
Diretoria Médica - Pesquisa Clinica - II Andar
Estrada Dos Bandeirantes, 8464
Jacarepagua
CEP: 22783-110
Rio de Janeiro, Brazil

~~Av. Insurgentes Sur 1605 piso 20,~~
~~Colonia San Jose Insurgentes~~
~~Mexico D.F.~~
~~CP04800~~
Calzada Mexico Xochimilco N° 4900
1er piso
Colonia San Lorenzo Huipulco
Delegacion Tlalpan
CP 14370, Mexico D.F.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Medical Monitor (Brazil)

[redacted] [redacted] M.D.
~~Av. Comandante Guaranys, 447~~
~~Jacarepagua, Rio de Janeiro~~
~~Brasil 22775-610~~
~~Tel:~~ [redacted]
~~Fax:~~ [redacted]
GlaxoSmithKline
Diretoria Médica - Pesquisa Clinica - II Andar
Estrada Dos Bandeirantes, 8464
Jacarepagua
CEP: 22783-110
Rio de Janeiro, Brazil
Tel: [redacted]
Fax: [redacted]

Medical Monitor (Mexico)

[redacted] M.D.
~~Av. Insurgentes Sur 1605 piso 20,~~
~~Colonia San Jose Insurgentes~~
~~Mexico D.F.~~
~~CP04800~~
~~Tel:~~ [redacted]
~~Fax:~~ [redacted]
Calzada Mexico Xochimilco N° 4900
1er piso
Colonia San Lorenzo Huipulco
Delegacion Tlalpan
CP 14370, Mexico D.F.
Tel: [redacted]
Fax: [redacted]

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Clinical Study Director [redacted] M.D.
~~Av. Comandante Guaranys, 447~~
~~Jacarepagua, Rio de Janeiro~~
~~Brasil 22775-610~~
~~Tel:~~ [redacted]
~~Fax:~~ [redacted]
GlaxoSmithKline
Diretoria Médica - Pesquisa Clinica - II Andar
Estrada Dos Bandeirantes, 8464
Jacarepagua
CEP: 22783-110
Rio de Janeiro, Brazil
Tel: [redacted]
Fax: [redacted]

Section 6.4

Randomisation of supplies

The enrolment in Mexico will be terminated by end December 2001 to avoid vaccinating subjects during the rotavirus season. Thus, no further subjects will be enrolled in Mexico after December 31, 2001. Enrolment of eligible subjects will continue in Venezuela and Brazil to compensate the lower recruitment in Mexico.

Section 8.5.2

Study Contact for Reporting Serious Adverse Events	
Brazil *Medical Monitor:* [redacted] MD ~~Av. Comandante Guaranys, 447~~ ~~Jacarepagua, Rio de Janeiro~~ ~~Brasil 22775-610~~ ~~Tel:~~ [redacted] ~~Fax:~~ [redacted] ***GlaxoSmithKline*** ***Diretoria Médica - Pesquisa Clinica - II Andar*** ***Estrada Dos Bandeirantes, 8464*** ***Jacarepagua*** ***CEP: 22783-110*** ***Rio de Janeiro, Brazil*** Tel: [redacted] Fax: [redacted]	Clinical Research Associate: [redacted] ~~Av. Comandante Guaranys, 447~~ ~~Jacarepagua, Rio de Janeiro~~ ~~Brasil 22775-610~~ ~~Tel:~~ [redacted] ~~or~~ [redacted] ~~Fax:~~ [redacted] ***GlaxoSmithKline*** ***Diretoria Médica - Pesquisa Clinica - II Andar*** ***Estrada Dos Bandeirantes, 8464*** ***Jacarepagua*** ***CEP: 22783-110*** ***Rio de Janeiro, Brazil*** Tel: [redacted] Fax: [redacted]
Mexico *Medical Monitor:* Dr. [redacted] ~~Av. Insurgentes Sur 1605 piso 20,~~ ~~Colonia San Jose Insurgentes~~ ~~Mexico D.F.~~ ~~CP04800~~ ~~Tel:~~ [redacted] ~~Fax:~~ [redacted] ***Calzada Mexico Xochimilco N° 4900*** ***1er piso*** ***Colonia San Lorenzo Huipulco*** ***Delegacion Tlalpan*** ***CP 14370, Mexico D.F*** Tel: [redacted]	*Clinical Research Associate:* [redacted] ~~Av. Insurgentes Sur 1605 piso 20,~~ ~~Colonia San Jose Insurgentes~~ ~~Mexico D.F.~~ ~~CP04800~~ ~~Fax:~~ [redacted] ***Calzada Mexico Xochimilco N° 4900*** ***1er piso*** ***Colonia San Lorenzo Huipulco*** ***Delegacion Tlalpan*** ***CP 14370, Mexico D.F***

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Fax: [redacted]	Fax: [redacted]

Appendix C

- . ***The enrolment in Mexico will be terminated by end December 2001 to avoid vaccinating subjects during the rotavirus season. Thus, no further subjects will be enrolled in Mexico after December 31, 2001. Enrolment of eligible subjects will continue in Venezuela and Brazil to compensate the lower recruitment in Mexico.***
- Target enrollment will be 2640 subjects ~~(approximately 1020 in Brazil; 800 in Mexico and 820 in Venezuela)~~.

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by:		
Director	[redacted]	dd-mm-yy
Head Biometrician	[redacted]	dd-mm-yy
Investigators	Dr. [redacted]	dd-mm-yy
	Dr. [redacted]	dd-mm-yy
	Dra. [redacted]	dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Amendment 3

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Rationale of the amendment:

This protocol was amended on **May 3, 2002** for the following major items:

- The results of an interim analysis of immunogenicity have shown that the immune response to the HRV vaccine after a two-dose regimen was lower than that observed previously in clinical studies conducted with this vaccine in Europe. The relevance of this lower response in terms of efficacy is unknown, since no serological correlates of protection are defined for rotavirus disease.

  The purpose of this amendment is to allow administration of a third dose of the HRV vaccine to a subset of 200 infants in order to assess whether a three-dose schedule can lead to a higher immune response. A blood sample will be drawn from this subset at two months after the second and the third dose of study vaccine or placebo.

- To decrease the sample size because of difficulty in enrolling eligible subjects for participation in the study. The new sample size will allow evaluation of the study objectives.

  The assessment of efficacy in protecting from rotavirus disease will be performed as planned originally in a cohort of about 2000 children who have received two doses of the HRV vaccine.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

The following strikethrough and bolded italic text were amended:

Synopsis (indication)

A subset of subjects (N = 200) will receive a third dose of the HRV vaccine at 6 months of age.

Synopsis (rationale) and Section 1.2

A third dose of the HRV vaccine will be administered to a sub-group of 200 infants in order to explore whether a 3-dose schedule can lead to a higher immune response.

Synopsis (primary objective) and Section 2.1

For the subset of subjects who receive two doses of HRV or placebo (N=2076)

Synopsis (secondary objectives) and Section 2.2

Efficacy

For the subset of subjects who receive two doses of HRV or placebo (N=2076):

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' …….

For the subset of subjects who receive three doses of HRV or placebo (N=200):

- ***To explore the rates of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end the efficacy follow-up period.***

Immunogenicity

For the subset of subjects who receive two doses of HRV or placebo (N=2076):

- To assess persistence of serum IgA to rotavirus at ~~Visit 4~~ ***the final visit.***

For the subset of subjects who receive three doses of HRV or placebo (N=200):

- ***To assess serum IgA to rotavirus, two months after dose 2 and dose 3 of study vaccine or placebo.***

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

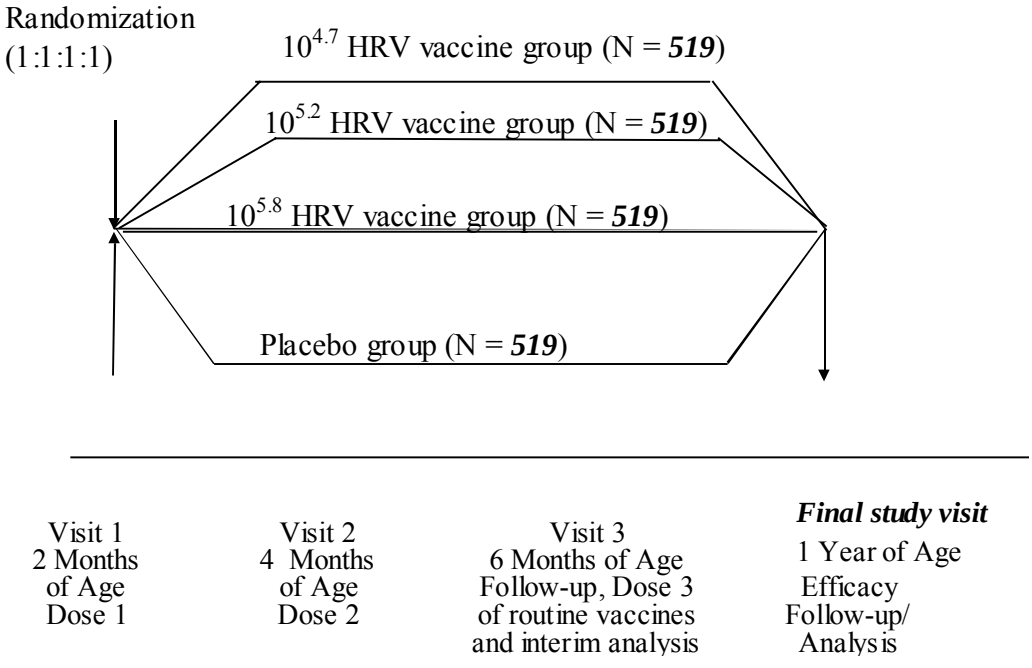
- ***To assess viral shedding in the vaccine groups after the third HRV vaccine dose.***
- ***To explore the effect of SB Biologicals' rotavirus vaccine on the immune response to concurrently administered routine vaccinations two months after the third dose of routine vaccines.***

Safety/Reactogenicity

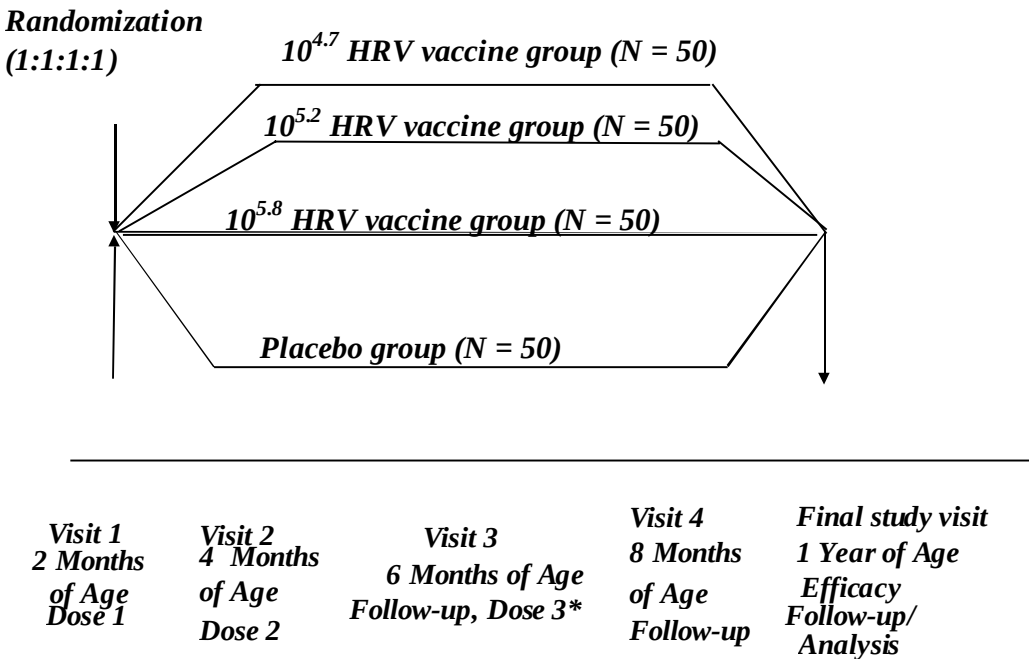
- ***To assess the safety and reactogenicity of the third dose of SB Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo in a subset of subjects (N=200).***

Section 3

For the subset of subjects who receive two doses of HRV or placebo:



For the subset of subjects who receive three doses of HRV or placebo:



***HRV vaccine/placebo and routine vaccines**

<u>Synopsis (study design) and Section 3</u>

- Indication:

  A subset of subjects (N = 200) will receive a third dose of the HRV vaccine at 6 months of age.
- Blinding: double-blind for HRV vaccine and placebo. The parents/guardians of the subjects and the study personnel will be blinded to the treatment administered. Blinding will be maintained for the whole study period (up to ***the final study visit*** that will take place approximately 10 months after study start). Refer to section 6.5.

Study Procedures

Final study visit (1 Year of Age) – Blood sample from subjects ***who receive two doses of study vaccine or placebo***, and Efficacy Follow-up.

A subset of subjects (N = 200) enrolled in Brazil and Venezuela will receive a third dose of the HRV vaccine or placebo along with blood sampling at Visit 3. A study visit (Visit 4) will take place for these subjects two months after the third dose of study vaccine or placebo to collect a blood sample and the final study visit will take place at approximately one year of age. A blood sample will not be taken from this subset at the final visit. These subjects will have 5 study visits in total.

- Active follow-up for safety and gastroenteritis via weekly visit to a subject by study personnel (Health Worker) starting 1 week after dose 1 and ending at ***the final study visit***.
- 15-day follow-up period (day 0 to day 14) on solicited symptoms (fever, fussiness / irritability, diarrhea, vomiting, loss of appetite and cough/runny nose) after any dose of study vaccine using diary cards ***(in a subset of 200 subjects after dose 3).***
- Blood samples will be drawn from all subjects at study Visits 1, ***from subjects receiving two doses of study vaccine or placebo at the final visit*** and in a subset (N = 800) at Visits 2 and 3. ***Blood samples will be drawn from the subset receiving three doses of study vaccine or placebo (N = 200) at Visit 3 (two months after dose 2) and Visit 4 (two months after dose 3).***
- ***Stool samples will be collected from the subset receiving three doses of study vaccine/placebo (N = 200) on the day of administration of dose 3 and on day 7 following dose 3 of study vaccine.***
- Recording of unsolicited symptoms within 42 days after dose 1, dose 2 ***(in all subjects)***, ***and dose 3 (in a subset of 200 subjects)*** of the study vaccines.
- If any G1 rotavirus is detected in the stool specimens between Visit 1 and Visit 3 ***(Visit 4 for the subset receiving three doses of study vaccine or placebo)***, vaccine virus will be …….

Synopsis (number of subjects) and Section 4.1

Target enrollment ~~will be~~ ***was planned at*** 2640 (660 subjects in each group) to obtain 2360 evaluable subjects (590 each group) for the analysis of the primary objective.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

However, the target sample could not be reached because of difficulty in enrolling eligible subjects for participation in the study. The final enrollment is of 2276 eligible subjects.

Synopsis (analyses)

The final analysis will be performed at the end of the efficacy follow-up period, after all enrolled subjects have completed ~~visit 4~~ ***the final study visit***. ***Two*** ~~An~~ interim analyses will be performed on immunogenicity …….

Section 4.4

4.4 Elimination criteria during the study up to Visit 3 ***(up to Visit 4 for the subset of 200 subjects receiving three doses of study vaccine/placebo)***

These elimination criteria should be also checked on the day of dose 3 of study vaccine/placebo in the subset of 200 subjects (at Visit 4 for the subset receiving three doses of study vaccine/placebo).

Section 4.5

4.5 Elimination criteria during the study from Visit 3 ***or Visit 4 (for the subset of 200 subjects receiving three doses of study vaccine/placebo) until the final study visit***

The following criteria should be checked at ***the final study visit for all subjects*** ~~visit 4~~.

Section 5.2

In a subset of 200 subjects the 3d dose of DTPw-HB/Hib will be given concomitantly with the third dose of study vaccine/placebo.

Surveillance of gastroenteritis and collection of stool samples

An active surveillance for gastroenteritis ~~efficacy~~ will be conducted via weekly visits to a subject by study personnel (Health Worker) starting 1 week after dose 1 and ending at ***the final study visit*** ~~Visit 4~~.

Section 5.3

Subjects ~~participating in each part of the study~~ ***who receive two doses of study vaccine*** will have four study visits. ***Subjects who receive three doses of study vaccine will have five study visits.*** The study procedures at each visit are outlined below.

Age	**2 months**	**4 months**	**6 months**	***8 months***	**1 year**
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	***VISIT 4 DOSE 3 SUBSET ONLY****	~~**VISIT 4**~~ **FINAL VISIT**
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2** ***MO 4***	***Post vacc 3 MO 6***	**Post vacc 2 MO *10***
Informed consent	•				
Medical history	•				
Check of inclusion criteria	•				
Check of exclusion criteria	•				
Check of elimination criteria		•	•	•	•
Check of contraindications	•	•	•		
Physical examination	•	•	•	•	•
Pre-vaccination body temperature	•	•	•		
Measure/record height and weight	•	•	•	•	•
Blood sampling	• (1 ml of blood)	• (1 ml of blood in a subset#)	• (3 mls of blood in a subset#) ***• (1 ml of blood in dose 3 subset*)***	***• (3 mls of blood in dose 3 subset*)***	• (3 mls of blood in a subset#, 1 ml ***for subjects receiving two doses***)
Randomisation	•				
Stool samples will be collected from a subset (N = 400) on the day of administration of dose 1 and dose 2 and on day 7 following each dose. ***Stool samples will be collected from a subset (N = 200) on the day of administration of dose 3 and on day 7 following dose 3***	•	•	•		
Study Vaccine	•	•	• ***(dose 3 subset*)***		
Routine Vaccination	•	•	•		
Daily post-vaccination recording of solicited symptoms (days 0–14) by parents/guardians	•	•	• ***(dose 3 subset*)***		
Collection of stool samples	•	•	•	• ***(dose 3 subset*)***	•

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Age	**2 months**	**4 months**	**6 months**	***8 months***	**1 year**
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	***VISIT 4 DOSE 3 SUBSET ONLY****	~~**VISIT 4**~~ **FINAL VISIT**
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2** ***MO 4***	***Post vacc 3 MO 6***	**Post vacc 2 MO *10***
Recording of solicited symptoms, non serious adverse events within 42 days after dose 1, dose 2 ***and dose 3 (in a subset)***, by investigator		•	•	• ***(dose 3 subset*)***	
Contact (field visit) every week	◊	◊	◊	◊	◊
Return of GE diary	•	•	•	• ***(dose 3 subset*)***	•
GE diary transcription		•	•	• ***(dose 3 subset*)***	•
Documentation of routine EPI vaccines	•	•	•	• ***(dose 3 subset*)***	•
Recording medication	•	•	•	• ***(dose 3 subset*)***	
Reporting of Serious Adverse Events occurring throughout the study period	•	•	•	• ***dose 3 (subset*)***	•
Study Conclusion					•

#Subset for immunogenicity evaluation (N = 800)
****Subset receiving three doses of study vaccine/placebo (N = 200)***

Intervals between study visits* ***for subjects receiving 2 doses of study vaccine/placebo will be as follows***

Interval	**Size of interval**
1 (Visit 1→Visit 2)	49 - 83 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→ ~~Visit 4~~ ***Final visit***)	160 - 200 days

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

*The date of the previous visit is the reference date.

Intervals between study visits* for subjects included in the subset receiving 3 doses of study vaccine/placebo will be as follows

Interval	*Size of interval*
1 (Visit 1→Visit 2)	*49 - 83 days*
2 (Visit 2→Visit 3)	*49 - 83 days*
3 (Visit 3→Visit 4)	*49 – 83 days*
4 (Visit 3→Final visit)	*160 - 200 days*

The date of the previous visit is the reference date.

Section 5.4

Visit 3: Dose 3 of routine vaccines and Follow-up	**6 Months of Age (49 to 83 days after 2nd vaccination)**

In addition, to the above mentioned study procedure, the following study procedures will be done at Visit 3 for the subset of 200 subjects enrolled in Brazil and Venezuela who receive three doses of study vaccine or placebo:

- ***Collection of blood sample for serology: a minimum of 1 mls of whole blood to provide a minimum of 0.5 mls of serum according to instructions in Appendix D.***
- ***Collection of a stool sample at the day of or 1 day prior to vaccination.***
- ***Administration of study vaccines:***
  - ***Oral administration of third dose of the study vaccine or placebo according to the guidelines set out in Section 6.2. Study vaccine must be given before the routine vaccines. If regurgitation occurs immediately (within 30 minutes) after administration, do not give another dose and record in the eCRF.***
- ***The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.***
- ***At the end of the 30 minutes of observation period, a diary card will be provided to the parents/guardians of the subjects who received the third dose***

of study vaccine/placebo to record body temperature (measured by a axillary/rectal route), the number of looser than normal stools passed by the subject, the number of vomiting episodes, any loss of appetite, any fussiness/irritability, any cough/runny nose during the 15-day solicited follow-up period, as well as unsolicited symptoms occurring within 42 days after dose 3.

- ***Recording the subject's feeding schedule for the subset who received the third dose of study vaccine/placebo. The parent/guardian will be questioned whether the child is fed with breast milk or infant formula and whether the child was fed within 60 minutes before vaccination and/or 30 minutes after vaccination.***

NOTE: Subjects receiving 3 doses of study vaccine or placebo will have Visit 4 approximately two months after Visit 3. Final study visit (Visit 5) for these subjects will take place approximately 4 months after.

Interval between Visit 3 and 4 for subjects included in the subset receiving 3 doses of study vaccine/placebo

Day 7 +/-1: collection of a stool sample

Day 0 to Day 14 (At bedtime):

- ***The following data will be recorded on the diary card:***
  - ***general solicited symptoms (fever, irritability/fussiness, diarrhea, vomiting, loss of appetite, cough/runny nose)***
  - ***unsolicited symptoms, including any SAE***

Interval between Visit 3 and ~~Visit 4~~ *final study visit*

Continued efficacy follow-up:

- Parents/guardians of all subjects will be instructed to collect one stool sample if they suspect that the subject has gastroenteritis symptoms (diarrhea) between Visits 3 and ~~4~~ ***final study visit***.

Visit 4 only for subjects receiving 3 doses of study	**8 Months of Age (49 to 83 days after Visit 3)**

vaccine/placebo: Follow-up

- ***Physical examination with measurement and recording of height and weight.***
- ***Check elimination criteria.***
- ***Recording previous/concomitant medication (see section 6.9).***
- ***Collection of blood sample for serology: a minimum of 3 mls of whole blood to provide a minimum of 1.5 mls of serum according to instructions in Appendix D.***
- ***Collection and verification of diary card containing information on adverse experiences occurring from Visit 3 until Visit 4. The investigator will verify the diary card(s) and transcribe the information into the appropriate sections of the eCRF, in English. The study monitor may help in this translation. Any unreturned diary cards will be sought through telephone call(s) or any other convenient procedure.***
- ***Recording of unsolicited adverse events that may have occurred on day 0-42 after dose 3.***
- ***Recording of serious adverse events that may have occurred since previous visit.***
- ***The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.***

***Final study visit (Visit 4 for subjects receiving 2 doses of study vaccine/placebo or Visit 5 for subjects receiving 3 doses of study vaccine/placebo)*: Efficacy Follow-up**	**1 Year of Age (160 – 200 days after Visit 3)**

- Collection of blood sample from subjects for serology: a minimum of 3 mls of whole blood for the subjects in the subset (800 subjects) and a minimum of 1 ml in ~~all other~~ subjects ***who received two doses of study vaccine or placebo***.

- Recording of diary card information on gastroenteritis episodes which occurred since ~~Visit 3~~ ***the previous visit***. The investigator will transcribe the information into the appropriate sections of the eCRF.
- Document the administration of routine EPI vaccines in the interval before ***the final visit***; there is no requirement to document vaccines administered at ***the final visit***.

Section 5.5.2

Stool analysis

Stool samples will be also collected from the subset receiving three doses of study vaccine/placebo (N = 200) on the day of or 1 day prior to administration of dose 3 and on day 7 following dose 3 of study vaccine.

Any detection of the vaccine virus in any stool collected after vaccination up to Visit 3 ***(Visit 4 for subset receiving three doses of study vaccine/placebo)*** will be taken ……

…***(Visit 4 for the subset receiving three doses of study vaccine or placebo)***,….

Immunogenicity

For all subjects, a minimum of 1 ml of whole blood will be collected at Visit 1. For subjects receiving two doses of HRV vaccine or placebo, for the immunogenicity subset (N=800), a minimum of 1 ml of whole blood will be collected at Visit ~~1 and~~ 2 and a minimum of 3 mls of whole blood will be collected at Visit 3 and ***at the final study visit***, using tubes with serum separator. For all other subjects ***receiving two doses of vaccine***, a minimum of 1 ml of whole blood will be collected ***at the final study visit***. ***For the subset receiving three doses of study vaccine/placebo (N = 200), a minimum of 1 ml of whole blood will be collected at Visit 3 and a minimum of 3 mls of whole blood will be collected at two months after dose 3 (Visit 4).***

Section 5.5.3

Study Group	Blood sampling timepoint			Antigen	No. subjects
	Timing	**Month**	**Visit no.**		
A, B, C & D	Pre	0	1	rotavirus only	~~2640~~ ***2276***
A, B, C & D	Post II MO 4	4	3	all ***rotavirus only***	800 ***200****
A, B, C & D	***Post III MO 6***	***6***	***4***	***all***	***200****
A, B, C & D	Post II MO 10	10	4 ***Final study visit***	all rotavirus only	800 ~~1840~~ ***1276#***

=subset of subjects who receive 3 doses of the study vaccine or placebo
#= only subjects who receive 2 doses of the study vaccine or placebo

Section 6.1.2

~~**One lot**~~ ***Two lots will be used.***

Section 6.2

Visit	Vaccination	Dose	Vaccine	Route[1]	Site[2]	Side
3 (Subset)	***Rotavirus***	***1***	***Human Rotavirus***	***Oral***	***NA***	***NA***

Section 6.4

The target sample size ~~is~~ ***was planned at*** 2640 enrolled subjects……

A subset of 200 subjects among the last enrolled in Brazil and Venezuela will constitute the subset that will receive three doses of study vaccine/placebo.

Section 6.9

Only at visit 1, 2, 3 ***(for all subjects) and at visit 4 (for the subset receiving three doses of study vaccine/placebo),*** the investigator should question the subject or their legal representative about any medication taken.

Any immunosuppressants or other immune-modifying drugs or treatments administered at ANY time during the period starting 30 days prior to the first dose of study vaccine(s) and ending at Visit 3 ***(Visit 4 for the subset of subjects receiving a third dose of study vaccine/placebo)*** must be …….. Any vaccine other than the study vaccine(s) administered at ANY time during the period starting at birth and ending at ~~Visit 4~~ ***the last study visit*** must be recorded …

Section 8

Surveillance period for occurrence of adverse events

All non-serious adverse events occurring within 42 days after ***each study vaccine/placebo*** dose ~~1 and dose 2~~ must ……

Section 8.5.2

Study Contact for Reporting Serious Adverse Events	
	Clinical Research Associate: [redacted] ***Cell:*** [redacted]

Section 9.1

From an analysis perspective, any subject who does not come back for ~~Visit 4~~ ***the final study visit*** is a drop-out for the efficacy analysis. A subject who returns for ~~Visit 4~~ ***the final study visit*** is considered to have completed….

Synopsis (primary endpoint) and Section 10.1

For the subset of subjects who receive two doses of HRV or placebo (N=2076).

- Occurrence……..

Synopsis (secondary endpoints) and Section 10.2

Efficacy

For the subset of subjects who receive two doses of HRV or placebo (N=2076)

- Occurrence of ……..

For the subset of subjects who receive three doses of HRV or placebo (N=200):

- ***Occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the efficacy follow-up period.***

Immunogenicity endpoints

For the subset of subjects who receive two doses of HRV or placebo (N=2076).

- Serum rotavirus IgA antibody titers at Visits 1 and 4 ***the final visit*** and at Visits 2 and 3 in a subset ***(N=800)***.
- Proportion of subjects with vaccine take at visits 2 and 3 in a subset ***(N=800)***.
- Viral shedding in the vaccine groups in a subset ***(N = 400)***.

Two months after dose 2 (at Visit 3) and at year 1 (at ~~Visit 4~~ ***final study visit)*** in a subset (800 subjects).

◊ GMTs for …….

For the subset of subjects who receive three doses of HRV or placebo (N=200):

- ***Serum rotavirus IgA antibody titers at visit 1, 3 and 4.***
- ***GMTs for anti-PRP, anti-diphtheria and anti-tetanus toxoids, anti-BPT, anti-polio types 1, 2 and 3 and anti-HBs two months after dose 3***
- ***Seroprotection status two months after dose 3:***
  - ◊ ***anti-PRP antibody concentrations ≥0.15 and ≥1.0 mcg/ml***
  - ◊ ***anti-diphtheria toxoid antibody concentrations ≥0.1 IU/ml***
  - ◊ ***anti-tetanus toxoid antibody concentrations ≥0.1 IU/ml***
  - ◊ ***anti-HBs antibody concentrations ≥10.0 mcg/ml***
  - ◊ ***anti-polio type 1 antibody titers ≥8***
  - ◊ ***anti-polio type 2 antibody titers ≥8***
  - ◊ ***anti-polio type 3 antibody titers ≥8***
- ***Seropositivity status two months after dose 3:***
  - ◊ ***anti-BPT antibody concentrations ≥15 EL.U/ml***
- ***Viral shedding in the vaccine groups on the day of and on day 7 after dose 3.***

Safety endpoints

- For each type of solicited symptoms, occurrence of the symptom within the 15-day solicited follow-up period after any dose of study vaccine ***(in a subset after dose 3.***
- Occurrence of unsolicited symptoms within 42 days after dose 1, dose 2 ***(in all subjects) and dose 3 (in a subset)***, according to WHO classification.

Section 10.3

The analysis of immunogenicity on the ATP cohorts will be the primary analyses. The analyses of the total cohort for immunogenicity ~~and efficacy~~ will only be performed if more than 5% of the enrolled subjects are excluded from the corresponding ATP cohort. In such case, the total cohort analyses will evaluate whether exclusion from the ATP cohorts could have biased the results.

The ATP efficacy cohort will be used for the primary analysis of efficacy. An analysis of efficacy based on the total cohort will also be performed.

The total cohort will be used for the primary analysis of safety. The analysis on the ATP cohort for safety will only be performed if more than 5% of the enrolled subjects are excluded from the ATP safety cohort.

The analyses of safety, immunogenicity and efficacy for the subset of subjects who received 3 doses of HRV or placebo will be performed on the total cohort.

Section 10.4

The target sample size ~~is~~ ***was*** planned at 2640 enrolled subjects to reach 2360 subjects in the ATP cohort of efficacy (590 in each group). ***However, the target sample size has been reduced because of difficulty in enrolling eligible subjects for participation in the study. In addition, a subset of 200 subjects will receive 3 doses of HRV vaccine or placebo. Target enrollment for subjects who will receive only 2 doses of HRV vaccine or placebo is estimated to be 2076 eligible subjects leaving 460 evaluable subjects per group for the analysis of the primary objective.***

Table 10.4-1 was updated with respect to the actual sample size.

Section 10.5

The final analysis will be performed at the end of the efficacy follow-up period, after all enrolled subjects have completed ~~visit 4~~ ***the final study visit***. ~~An~~ ***Two*** interim analyses will be performed ….

Section 10.5.3

For the subset of subjects who received 2 doses of HRV or placebo:

In addition, for all antigens, the distribution of antibody titers two months after the second dose and at ~~Visit 4~~ ***the final study visit*** will be displayed ……

Difference between each vaccine group and placebo ***two*** months….

For the subset of subjects who received 3 doses of HRV or placebo:

The distribution of antibody titers two months after the second dose (rotavirus only) and after the third dose (all antigens) will be displayed using reverse cumulative curve.

Section 10.5.4

The vaccine efficacy rate (VE) ***for subjects who received 2 doses of HRV vaccine or placebo***, expressed as ……

For the subset of subjects who receive 3 doses of HRV or placebo:

- ***the proportion of subjects reporting any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the efficacy follow-up period will be calculated by group and for pooled vaccine groups. An episode of gastroenteritis will be classified positive for rotavirus if the stool samples collected during the episode are positive as tested by Rota Ag ELISA.***

Section 10.6

No study report will be written for the interim data and results will be ***strictly controlled*** ~~kept in house~~.

An interim analysis will be performed on post-dose 3 data. This analysis will present a descriptive summary of immunogenicity and reactogenicity for the study vaccine as well as immunogenicity data for routine vaccines. No study report will be written for the interim data and results will be kept in house. Unblinding at the level of individual data will be restricted to the statistician and the database administrator.

The results of interim analyses performed on post-dose 2 and post-dose 3 data may be presented at scientific conferences and, as required, to the authorities.

Appendix C

- Target enrollment ~~will be~~ ***was planned at*** 2640 subjects. ***Final enrolment is 2276 subjects enrolled as follows: 405 in Mexico, 972 in Venezuela and 899 in Brazil***.

Appendix G

The following represents the vaccine supplies that will be provided to administer the third dose of study vaccine/placebo to the subset of 200 subjects including 20% over-randomisation:

- ***approximately 60 doses of the $10^{4.7}$ HRV vaccine***
- ***approximately 60 doses of the $10^{5.2}$ HRV vaccine***
- ***approximately 60 doses of the $10^{5.8}$ HRV vaccine***
- ***approximately 60 doses of the placebo***
- ***240 doses of the diluent***

Appendix M

Appendix M was added to the protocol for supplemental subject information and informed consent for study participants who will receive three doses of study vaccine/placebo.

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Date of amendment 3	**May 3, 2002**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Approved by:		
Director	[redacted]	dd-mm-yy
Head Biometrician	[redacted]	dd-mm-yy
Investigators	Dr. [redacted]	dd-mm-yy
	Dr. [redacted]	dd-mm-yy
	Dra. [redacted]	dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Amendment 4

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Rationale of the amendment:

This protocol was amended on **July 11, 2002,** to perform an interim analysis in order to provide early information on the efficacy of the HRV vaccine against any and severe rotavirus gastroenteritis in Latin America.

This interim efficacy analysis will not have any impact on the follow-up of subjects nor on the statistical power for the final analysis.

The following strikethrough and bolded italic text were amended:

Synopsis (analyses)

An interim analysis on efficacy against any and severe rotavirus gastroenteritis will be performed to obtain early efficacy data.

The results of ***all*** interim analyses may be presented at scientific conferences and, as required, to the authorities.

Section 10.6

An interim analysis on efficacy against any and severe rotavirus gastroenteritis will be performed to obtain early efficacy data. The interim efficacy analysis will be performed during the efficacy follow-up period, when a number of rotavirus gastroenteritis cases is reached that will allow to demonstrate vaccine efficacy (with LL of 95CI > 0) with 75% power based on the following conservative assumptions: vaccine efficacy (for pooled HRV vaccine groups)

against any rotavirus gastroenteritis is 50%, with an attack rate of 6% in the placebo group. No study report will be written for the interim efficacy data and distribution of the results will be strictly controlled. Unblinding at the level of individual data will be restricted to the statistician and the database administrator.

Table 10.6-1 indicates the level of accuracy that can be expected for the interim evaluation of efficacy against any rotavirus and severe rotavirus gastroenteritis above a specific cut-off.

Table 10.6-1: Power to get an exact 95% CI for the interim vaccine efficacy analysis (pooled vaccine groups versus placebo) above a specific cut-off (460 evaluable subjects per group, power based on 1.000 simulations using Proc StatXact)

% of subjects reporting rotavirus gastroenteritis in the placebo group	*% of subjects reporting rotavirus gastroenteritis in pooled vaccine groups*	*Efficacy (%)*	*Cut-off*
			0%
Any Gastroenteritis			
6%	*1.8%*	*70%*	*97%*
6%	*2.4%*	*60%*	*89%*
6%	*3.0%*	*50%*	*75%*
5%	*1.5%*	*70%*	*96%*
5%	*2.0%*	*60%*	*86%*
5%	*2.5%*	*50%*	*65%*
Severe Gastroenteritis			
3%	*0.9%*	*70%*	*82%*
2%	*0.4%*	*80%*	*79%*
2%	*0.6%*	*70%*	*60%*
2%	*0.8%*	*60%*	*45%*

No adjustment on the alpha or the power will be applied for the final analyses of efficacy.

The results of interim analyses performed on post-dose 2, ***interim efficacy data*** and post-dose 3 data may be presented at scientific conferences and, as required, to the authorities.

Appendix E

~~Gastroenteritis stool samples have to be sent as infectious substances.~~

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Date of amendment 3	May 3, 2002
Date of amendment 4	**July 11, 2002**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Approved by: Clinical Development Manager	[redacted]	dd-mm-yy
Head Biometrician	[redacted]	dd-mm-yy
Investigators	Dr. [redacted]	dd-mm-yy
	Dr. [redacted]	dd-mm-yy
	Dra. [redacted]	dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Amendment 5

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Rationale of the amendment:

This protocol was amended on **September 20, 2002** for the following:

- An interim efficacy analysis has demonstrated the efficacy of the HRV vaccine in preventing rotavirus gastroenteritis in infants after a two-dose regimen.

  The purpose of this amendment is to add a second year of efficacy follow-up (until age 24 months) for the subjects (N = approximately 1000 subjects) who have not completed the study as of October 31, 2002 in order to assess the efficacy during the second efficacy follow-up period.

The following strikethrough and bolded italic text were amended:

Definitions

Efficacy follow-up period: Each subject will be followed for the efficacy analysis starting from two weeks post dose 2 until the age of approximately one year ***(approximately two years for a subset of about 1000 subjects)***.

<u>Section 1.2</u>

Protective efficacy will be evaluated in all enrolled subjects until they reach one year of age. Efficacy during a second year will be evaluated in a subset of children (about 1000).

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Synopsis (primary objective) and Section 2.1

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' HRV vaccine, to demonstrate the efficacy of two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations in preventing any rotavirus gastroenteritis* during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period.

Synopsis (secondary objectives) and Section 2.2

Efficacy

First year follow-up

For the subset of subjects who receive two doses of HRV or placebo (N=2076):

- Prevent severe rotavirus gastroenteritis during-the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Prevent rotavirus gastroenteritis due to virus types heterologous to vaccine strain ***from two weeks after dose 2 until the end of the first efficacy follow-up period***. (amended: 12-FEB-2001)
- Prevent any and severe pure rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Prevent mixed rotavirus gastroenteritis (gastroenteritis associated with rotavirus and at least one other pathogen) during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Prevent any hospitalization for rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period (see section 8.5.1 for definition of hospitalization).

For the subset of subjects who receive three doses of HRV or placebo (N~200):

- To explore the rates of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the ***first*** efficacy follow-up period.

Second year follow-up (for a subset of about 1000 subjects)

- ***To evaluate the efficacy of the HRV vaccine during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period, and during the period starting from 2 weeks after the last HRV/placebo dose until the end of the second efficacy follow-up period.***

  The endpoints evaluated for this second year analysis (severity and nature of disease, study groups and subsets) will be similar to those evaluated during the first year of follow-up (refer to section 10.5.4 for details).

Immunogenicity

For the subset of subjects who receive two doses of HRV or placebo (N=2076):

- To assess persistence of serum IgA to rotavirus at the ***end of the first efficacy follow-up period*** ~~final visit~~.

Synopsis (analyses)

The final analysis will be performed at the end of the ***first*** efficacy follow-up period, after all enrolled subjects have completed the ***study visit at the end of the first follow-up period***. ***Analysis of data collected during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be presented in an annex.***

Synopsis (study procedures) and Section 3

- ***All subjects will be followed for efficacy until one year of age and a subset, about 1000 subjects, will be followed for efficacy until two years of age.***
- ***For the subjects who participate only in the first year of efficacy follow-up (until age 12 months),*** the intended duration of the study, per subject, will be approximately 10 months for subjects. ***For the subset of subjects who participate in a second year of efficacy follow-up (until age 24 months), the intended duration of the study, per subject, will be approximately 22 months.***

Study Procedures

- Study visits:

Study visit ***at the end of the first efficacy follow-up period*** (1 Year of Age) – Blood sample from subjects who receive two doses of study vaccine or placebo, and Efficacy Follow-up. ***This will be the final study visit for the subjects who participate only in the first year of efficacy follow-up.***

A subset of subjects (N ~ 200) enrolled in Brazil and Venezuela will receive a third dose of the HRV vaccine or placebo along with blood sampling at Visit 3. A study visit (Visit 4) will take place for these subjects two months after the third dose of study vaccine or placebo to collect a blood sample. For these subjects the first ***efficacy follow-up*** study visit will take place at approximately one year of age: a blood sample will not be taken from this subset at ***this visit***. ~~These subjects will have 5 study visits in total.~~.

Study visit at the end of the second efficacy follow-up period (2 Years of Age) – Efficacy Follow-up. This will be the final study visit for the subjects who participate in a second year of efficacy follow-up.

- Active follow-up for safety and gastroenteritis via weekly visit to a subject by study personnel (Health Worker) starting 1 week after dose 1 and ending at the study visit ***at the end of the second efficacy follow-up period***. ***For the subjects who participate only in the first year of efficacy follow-up, active follow-up for safety and gastroenteritis via weekly visit to a subject by study personnel (Health Worker) will end at the study visit at the end of the first efficacy follow-up period.***
- Blood samples will be drawn from all subjects at study Visits 1, from subjects receiving two doses of study vaccine or placebo at the ***end of the first efficacy follow-up period*** ~~final visit~~ and in a subset (N = 800) at Visits 2 and 3. Blood samples will be drawn from the subset receiving three doses of study vaccine or placebo (N ~ 200) at Visit 3 (two months after dose 2) and Visit 4 (two months after dose 3).

<u>Section 4.5</u>

4.5 Elimination criteria during the study from Visit 3 ~~or~~ (*from* Visit 4 ~~(~~for the subset of 200 subjects receiving three doses of study vaccine/placebo) until the ~~final study visit~~ study end

The following criteria should be checked at the ***follow-up visit at the end of the first efficacy follow-up period and at the end of the second efficacy follow-up period as applicable*** ~~final study visit for all subjects~~.

Section 5.2
Surveillance of gastroenteritis and collection of stool samples

For the subjects who participate only in the first year of efficacy follow-up, the follow-up visit at the end of the first efficacy follow-up period (at 1 year of age) will be the final visit. For the subjects who participate in a second year of efficacy follow-up, the follow-up visit at the end of the second efficacy follow-up period (at 24 months of age) will be the final visit.

Section 5.3
All subjects who have not completed the follow-up visit at 1 year of age as of October 31, 2002, will have an additional follow-up visit at approximately 24 months of age. The number of subjects in this case is expected to be about 1000.

Age	**2 months**	**4 months**	**6 months**	**8 months**	***1 year***	***2 years***
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4 DOSE 3 SUBSET ONLY***	***END OF 1ST EFFICACY PERIOD***	***END OF 2ND EFFICACY PERIOD***
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 MO 4**	**Post vacc 3 MO 6**	**Post vacc 2 MO 10**	***Post vacc 2 MO 22***
Informed consent	•					
Medical history	•					
Check of inclusion criteria	•					
Check of exclusion criteria	•					
Check of elimination criteria		•	•	•	•	•
Check of contraindications	•	•	•			
Physical examination	•	•	•	•	•	•
Pre-vaccination body temperature	•	•	•			
Measure/record height and weight	•	•	•	•	•	•
Blood sampling	• (1 ml of blood)	• (1 ml of blood in a subset#)	• (3 mls of blood in a subset#) • (1 ml of blood in dose 3 subset*)	• (3 mls of blood in dose 3 subset*)	• (3 mls of blood in a subset#, 1 ml for subjects receiving two doses)	
Randomisation	•					
Stool samples will be collected from a subset (N = 400) on the day of administration of dose 1 and dose 2 and on day 7 following each dose. Stool samples will be collected from a subset (N ~ 200) on the day of administration of dose 3 and on day 7 following dose 3	•	•	•			
Study Vaccine	•	•	• (dose 3 subset*)			
Routine Vaccination	•	•	•			
Daily post-vaccination recording of solicited symptoms (days 0–14) by parents/guardians	•	•	• (dose 3 subset*)			
Collection of stool samples ***if the child is suspected to have gastroenteritis***	•	•	•	•	•	•

Age	**2 months**	**4 months**	**6 months**	**8 months**	***1 year***	***2 years***
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4 DOSE 3 SUBSET ONLY***	***END OF 1ST EFFICACY PERIOD***	***END OF 2ND EFFICACY PERIOD***
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 MO 4**	**Post vacc 3 MO 6**	**Post vacc 2 MO 10**	***Post vacc 2 MO 22***
Recording of solicited symptoms, non serious adverse events within 42 days after dose 1, dose 2 and dose 3 (in a subset), by investigator		•	•	• (dose 3 subset*)		
Contact (field visit) every week	◊	◊	◊	◊	◊	◊
Return of GE diary	•	•	•	• (dose 3 subset*)	•	•
GE diary transcription		•	•	• (dose 3 subset*)	•	•
Documentation of routine EPI vaccines	•	•	•	• (dose 3 subset*)	•	•
Recording medication	•	•	•	• (dose 3 subset*)		
Reporting of Serious Adverse Events occurring throughout the study period	•	•	•	• dose 3 (subset*)	•	•
Study Conclusion					•¶	•§

#Subset for immunogenicity evaluation (N = 800)
*Subset receiving three doses of study vaccine/placebo (N = 200)
◊ is used to indicate a study procedure which does not require documentation in the individual eCRFs.
¶For subjects who participate only in the first year of efficacy follow-up
§For subjects who participate in a second year of efficacy follow-up

Interval	**Size of interval**
1 (Visit 1→Visit 2)	49 - 83 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→ ***First efficacy follow-up visit***)	160 - 200 days
4 (First efficacy follow-up visit	***335–395 days***

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

→ Second efficacy follow-up visit)	

*The date of the previous visit is the reference date.

Interval	Size of interval
1 (Visit 1→Visit 2)	49 - 83 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→Visit 4)	49 – 83 days
4 (Visit 3→ ***First efficacy follow-up visit***)	160 - 200 days
5 (First efficacy follow-up visit → Second efficacy follow-up visit)	***335–395 days***

*The date of the previous visit is the reference date.

Section 5.4

Visit 3: Dose 3 of routine vaccines and Follow-up	**6 Months of Age (49 to 83 days after 2nd vaccination)**

These subjects will be followed until 2 years of age (all of them), thus the final visit will be at end of second efficacy follow-up (24 months of age). ~~Final study visit (Visit 5) for these subjects will take place approximately 4 months after.~~

Interval between Visit 3 and *end of the first efficacy follow-up period*

First efficacy follow-up visit **(Visit 4 for subjects receiving 2 doses of study vaccine/placebo or Visit 5 for subjects receiving 3 doses of study vaccine/placebo): Efficacy Follow-up**	**1 Year of Age (160 – 200 days after Visit 3)**

- Document the administration of routine EPI vaccines since the previous visit ~~in the interval before the final visit; there is no requirement to document vaccines administered at the final visit~~.

- Study Conclusion ***for the subjects who participate only in the first year of efficacy follow-up***.

Interval between end of the first efficacy follow-up period* and *end of the second efficacy follow-up period visits

Continued efficacy follow-up:

- ***A Health Worker will visit the parent/guardian weekly (except for weeks when a study clinic visit is scheduled) to assess the completion or collection of diary card information, check on the occurrence of SAE or gastroenteritis episodes and if appropriate, collect stool samples.***
- ***Parents/guardians of all subjects will be instructed to collect one stool sample if they suspect that the subject has gastroenteritis symptoms (diarrhea). A second stool sample will be collected on a different day if the first stool sample was insufficient. Two occurrences of gastroenteritis symptoms should be classified as separate episodes if there are 5 or more symptom-free days between the episodes. The study personnel may organise transportation of the stool samples.***
- ***Diary cards will also be provided to the parents/guardians of all subjects to daily record the following information until symptoms resolve during each suspected episode of gastroenteritis occurring between visits: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. Rehydration or other medication will be recorded.***

Second efficacy follow-up visit: Efficacy Follow-up	***2 Year of Age (335–395 days after first efficacy follow-up visit)***

- ***Physical examination with measurement and recording of height and weight.***
- ***Check elimination criteria.***
- ***Recording of diary card information on gastroenteritis episodes which occurred since the previous visit. The investigator will transcribe the information into the appropriate sections of the eCRF.***

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

- ***Recording of serious adverse events that may have occurred since previous visit.***
- ***Document the administration of routine EPI vaccines since the previous visit.***
- ***Study Conclusion for the subjects who participate in the second year of efficacy follow-up.***

Section 5.2

Stool Analysis

Also, stool samples will be collected during each episode of gastroenteritis which occur from the first dose until ***2*** years of age.

Immunogenicity

For subjects receiving two doses of HRV vaccine or placebo, for the immunogenicity subset (N=800), a minimum of 1 ml of whole blood will be collected at Visit 2 and a minimum of 3 mls of whole blood will be collected at Visit 3 and at the ***end of the first efficacy follow-up period*** ~~final study~~ visit, using tubes with serum separator.

Section 5.5.3

Study Group	Blood sampling timepoint			Antigen	No. subjects
	Timing	Month	Visit no.		
A, B, C & D	Post II	10	***End of 1st efficacy period visit***	all	800

Section 6.4

Subset Definitions

All subjects who have not completed the follow-up visit at 1 year of age as of October 31, 2002, will have an extended follow-up for rotavirus gastroenteritis

for one more year with an additional follow-up visit at approximately 24 months of age. The number of subjects in this case is expected to be approximately 1000.

Section 8.1.2

Subjects enrolled in this study will be followed from the day of first vaccination until ***2*** years of age for the occurrence of gastroenteritis.

Synopsis (primary endpoint) and Section 10.1

- Occurrence of any rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period.

Synopsis (secondary endpoints) and Section 10.2

Efficacy endpoints

For the subset of subjects who receive two doses of HRV or placebo (N=2076).

- Occurrence of severe rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Occurrence of rotavirus gastroenteritis due to virus types heterologous to vaccine strain during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Occurrence of any and severe pure rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Occurrence of rotavirus gastroenteritis in which there is at least one other pathogen during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Occurrence of hospitalization for rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.

For the subset of subjects who receive three doses of HRV or placebo (N~200):

- Occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the ***first*** efficacy follow-up period.

For the subset of subjects who participate in a second year of efficacy follow-up (until age 24 months):

- ***For the subset of subjects who receive two doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.***
- ***For the subset of subjects who receive two doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the second efficacy follow-up period.***
- ***For the subset of subjects who receive three doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.***
- ***For the subset of subjects who receive three doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the second efficacy follow-up period***.

Immunogenicity endpoints

For the subset of subjects who receive two doses of HRV or placebo (N=2076).

- Serum rotavirus IgA antibody titers at Visit 1 and the ***end of the first efficacy follow-up period*** ~~final~~ visit and at Visits 2 and 3 in a subset (N=800).

<u>Section 10.3</u>
ATP cohort for efficacy

The ATP cohort for efficacy will be used to evaluate efficacy and the persistence of immune response at the ***end of the first efficacy follow-up period*** ~~final~~ ~~study~~ visit.

Section 10.4

The primary objective is to demonstrate that, for a range of viral concentration ($10^{4.7}$-ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' HRV vaccine, two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations can prevent rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period following vaccination.

With respect to the year 2 efficacy follow-up, considering an attack rate of 12% for any gastroenteritis, a 60% VE and a sample size of 200 in each vaccine group, the power to detect a statistically significant vaccine effect with the pooled vaccine group and each vaccine group is 88% and 67% (2 sided fisher exact test, alpha=5%, no adjustment for multiplicity

Section 10.5

The final analysis will be performed at the end of the ***first*** efficacy follow-up period, after all enrolled subjects have completed the study visit ***at the end of the first efficacy follow-up period.*** Two interim analyses will be performed on immunogenicity and reactogenicity of the vaccines to provide early information on dose selection. ***An interim analysis on efficacy against any and severe rotavirus gastroenteritis will be performed to obtain early efficacy data.*** The interim results will be ***descriptive*** limited to summaries by group.

Analysis of data collected during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be presented in an annex.

Section 10.5.3

In addition, for all antigens, the distribution of antibody titers two months after the second dose and at ***the end of the first efficacy follow-up period*** ~~final~~ study visit will be displayed using reverse cumulative curves.

Section 10.5.4

Efficacy in the first efficacy follow-up period

The vaccine efficacy rate (VE) for subjects who received 2 doses of HRV vaccine or placebo, expressed as 100% X (1-Relative Risk), will be calculated for pooled vaccine groups and for each vaccine group, with their 95% CI (see Appendix J for mathematical detail) against:

- any and severe rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period,
- rotavirus gastroenteritis due to virus types heterologous to vaccine strain ***occurring two weeks after dose 2 until the end of the first efficacy follow-up period***. (amended: 12-FEB-2001)
- any and severe pure rotavirus gastroenteritis occurring two weeks after dose 2 until the end of the ***first*** efficacy follow-up period,
- mixed rotavirus gastroenteritis occurring during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period,
- any hospitalization for rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period,

The primary objective is to demonstrate that pooled HRV vaccine groups can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period, and subsequently that the HRV vaccine with a viral concentration of $10^{5.8}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period, and subsequently that the HRV vaccine with a viral concentration of $10^{5.2}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period, and subsequently that the HRV vaccine with a viral concentration of $10^{4.7}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.

The efficacy of the pooled vaccine groups will be first evaluated. If the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period following vaccination in the pooled HRV groups is statistically significantly lower than in the placebo group (two-sided Fisher Exact test: $p < 0.05$), one will conclude that the efficacy of the pooled HRV vaccine groups in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period has been demonstrated.

If in addition the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period following vaccination in the HRV group with a viral concentration of $10^{5.8}$ ffu is statistically significantly lower than in the placebo group (two-sided Fisher Exact test : $p < 0.05$), one will conclude that the efficacy of the HRV vaccine with a viral concentration of $10^{5.8}$ ffu in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period has also been demonstrated.

And, if in addition the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period following vaccination in the HRV group with a viral concentration of $10^{5.2}$ ffu is statistically significantly lower than in the placebo group (two-sided Fisher Exact test : $p < 0.05$), one will conclude that the efficacy of the HRV vaccine with a viral concentration of $10^{5.2}$ ffu in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period has also been demonstrated.

And, if in addition the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period following vaccination in the HRV group with a viral concentration of $10^{4.7}$ ffu is statistically significantly lower than the placebo group (two-sided Fisher Exact test: $p < 0.05$), one will conclude that the efficacy of the HRV vaccine with a viral concentration of $10^{4.7}$ ffu in preventing rotavirus

gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period has also been demonstrated.

For the subset of subjects who receive 3 doses of HRV or placebo:
the proportion of subjects reporting any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the ***first*** efficacy follow-up period will be calculated by group and for pooled vaccine groups.

Efficacy in the second efficacy follow-up period

The vaccine efficacy rate

- ***from the end of the first efficacy period up to the end of the second efficacy period***
- ***from two weeks post last HRV/placebo dose up to the end of the second efficacy period***

will be calculated for the pooled vaccine groups and for each vaccine group, with their 95% CI.

More specifically, this will be done for

- ***any (severe and hospitalized, respectively) rotavirus gastroenteritis,***
- ***any (severe and hospitalized, respectively) rotavirus gastroenteritis due to G1 types***
- ***any (severe and hospitalized, respectively) rotavirus gastroenteritis due to virus types heterologous to vaccine strain***

provided the number of cases is sufficient.

The above analyses will be performed separately for the subgroup of subjects enrolled in the 2-vaccine-dose cohort and the subgroup of subjects enrolled in the 3-vaccine-dose cohort.

Appendix N

Appendix N was added to the protocol for supplemental subject information and informed consent for study participants who will be followed until the end of the second efficacy follow-up period.

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Date of amendment 3	May 3, 2002
Date of amendment 4	July 11, 2002
Date of amendment 5	**September 20, 2002**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Approved by:		
Clinical Development Manager	[redacted]	dd-mm-yy
Head Biometrician	[redacted]	dd-mm-yy
Investigators		
	Dr. [redacted]	dd-mm-yy
	Dr. [redacted]	dd-mm-yy
	Dra. [redacted]	dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium
Protocol Amendment Approval
Rota-006
444563/006

Protocol Title: A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Amendment 6
Date 26 March 2003

Coordinating Author: [redacted] Scientific Writer

Rationale/background for changes: This amendment was done

- to implement the use of a 'Standard Verbal Autopsy Questionnaire' as per the IDMC's recommendation,
- to remove co-pathogen testing for all subjects during the second year of efficacy follow-up,
- to reflect the termination of follow-up of Mexican subjects after the end of the 2003 rotavirus season in Mexico and
- to reflect the interim analysis planned on efficacy assessment in the second year in Mexico.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

The following items in bold italics were amended on 26 March 2003:

Synopsis:

Rationale

Efficacy during a second year ***of efficacy follow-up period*** will be evaluated in a subset of children (about 1000).

Study Design

For the subset of subjects who participate in a second year of efficacy follow-up (until age ***18 -*** 24 months), the intended duration of the study, per subject, will be approximately ***16 -*** 22 months.

Study Procedure

A subset of subjects (N ~ 200) enrolled in Brazil ~~and Venezuela~~ will receive a third dose of the HRV vaccine or placebo along with blood sampling at Visit 3

Study visit at the end of the second ***year of*** efficacy follow-up ~~period (2 Years of Age~~ ***approximately 18 – 24 months of age***).

For the subset of subjects who participate in a second year of efficacy follow-up (until age 18 – 24 months)

Analyses

~~An~~ **Two** interim analysis on efficacy against any and severe rotavirus gastroenteritis will be performed to obtain early efficacy data.

Definitions

Second year of efficacy follow-up period: approximately 1000 subject will be followed for a second efficacy analysis either until the age of two years (for subjects from Brazil and Venezuela) or until the end of the 2003 rotavirus season (for subjects from Mexico)

Table of contents

ANNEX 1 (provided as a separate pdf document): The Standard Verbal Autopsy Questionnaire

Glossary of terms:

First year of **efficacy follow-up period:** Each subject will be followed for the

efficacy analysis starting from two weeks post dose 2 until the age of approximately one year ~~(approximately two years for a subset of about 1000 subjects)~~.
Second year of efficacy follow-up period: Approximately 1000 subject will be followed for a second efficacy analysis either until the age of two years (for subjects from Brazil and Venezuela) or until the end of the 2003 rotavirus season (for subjects from Mexico).

Rationale:
Efficacy during a second year ***of efficacy follow-up period*** will be evaluated in a subset of children (about 1000).

Section 3:
A subset of subjects (N ~ 200) enrolled in Brazil ~~and Venezuela~~ will receive a third dose of the HRV vaccine or placebo along with blood sampling at Visit 3

For the subset of subjects who participate in a second year of efficacy follow-up (until age ***18 -*** 24 months), the intended duration of the study, per subject, will be approximately ***16 -*** 22 months.

For these subjects the first ***year of*** efficacy follow-up study visit will take place at approximately one year of age: a blood sample will not be taken from this subset at this visit. (amended: 3-MAY-2002) (amended: 20-SEP-2002)
Study visit at the end of the second ***year of*** efficacy follow-up ~~period~~ (~~2 Years of Age~~ ***approximately 18 – 24 months of age***)

Section 5.3:

Table : ~~**Post vacc 2 MO 22,**~~ ***18 – 24 Mo***

Size of Interval **Brazil & Venezuela:335–395 days**
Mexico: June 1 -> 30, 2003 (after the end of rotavirus season)

Section 5.4:
~~**2 Year of Age**~~ **18 – 24 months of age (Brazil and Venezuela: 335–395 days after first efficacy follow-up visit) (Mexico : June 1 -> 30, 2003 after the end of RV season)**

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Section 5.5.2
During the first year of life, if rotavirus is detected (by rapid rotavirus detection kit) in the stool sample, part of the stool sample should be analysed locally for culture of enteric pathogens such as Salmonella, Shigella, and Campylobacter. ***During the second year of efficacy follow-up, the stool samples will be tested only for rotavirus, there will be no local testing for the presence of enteric pathogens.***

Section 5.5.3:

Study Group	Blood sampling timepoint			Antigen	No. subjects
	Timing	Month	Visit no.		
A, B, C & D	Post II MO 10	10	End of 1st efficacy period visit	~~all~~ ***concomitant*** rotavirus ~~only~~	800 ~~1276~~ ***2155***#

Section 6.4:
All subjects who have not completed the follow-up visit at 1 year of age as of October 31, 2002, will have an extended follow-up for rotavirus gastroenteritis for one more year with an additional follow-up visit at approximately ***18*** **-** 24 months of age.
In all, the subset that provides additional blood samples will contain ***approximately 800*** subjects and the subset that provides stool samples on day 0 and day 7 will contain ***approximately*** 400 subjects. (amended: 12-FEB-2001).

A subset of approximately 200 subjects among the last enrolled in Brazil ~~and Venezuela~~ will constitute the subset that will receive three doses of study vaccine/placebo. (amended: 3-MAY-2002). ***The sub-group that receives 3 doses is constituted of about 121 subjects (and not 200 as mentioned above) as the protocol was not approved in Venezuela. As outlined in the study procedures, these subjects also provide stool samples.***

Section 8.1.2
Subjects enrolled in this study will be followed from the day of first vaccination until ~~2 years of age~~ study end for the occurrence of gastroenteritis.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Section 8.5.2:
The Standard Verbal Autopsy Questionnaire (see Annex 1) (19) should be completed and transmitted by the investigator (or designee), in addition to the SAE report, for all deaths during the study period irrespective of relationship to vaccination and whether a written autopsy is performed or not. The Standard Verbal Autopsy Questionnaire does not replace the written autopsy. Refer to Annex 1.

[redacted]

Section 10.2:
For the subset of subjects who participate in a second year of efficacy follow-up (until age 18 - 24 months)

First year of *efficacy follow-up period*: Each subject will be followed for the efficacy analysis starting from two weeks post dose 2 until the age of approximately one year ~~(approximately two years for a subset of about 1000 subjects)~~.

Second year of efficacy follow-up period: approximately 1000 subject will be followed for a second efficacy analysis either until the age of two years (for subjects from Brazil and Venezuela) or until the end of the 2003 rotavirus season (for subjects from Mexico)

Section 10.5:
~~An~~ **Two** interim ~~analysis~~ **analyses** on efficacy against any and severe rotavirus gastroenteritis will be performed to obtain early efficacy data.

Section 10.6
An interim analysis on efficacy against any and severe rotavirus gastroenteritis at the end of the second efficacy follow-up period in Mexico will be performed to obtain early efficacy data. No study report will be written and distribution of the results will be strictly controlled. Unblinding at the level of individual data will be restricted to the statistician and the database administrator. No adjustment on the alpha or the power will be applied for the final analyses of efficacy. Considering an attack rate of 12% for any rotavirus gastroenteritis over the two

efficacy follow-up periods, a 60% VE and a sample size of 60 subjects in each group, the power to detect a statistically significant vaccine effect with the pooled vaccine group is 40% (2 sided fisher exact test, alpha=5%)

References:

World Health Organization. A Standard Verbal Autopsy Method for Investigating Causes of Death in Infants and Children. Geneva: World Health Organizatoin, 1999:1-78. (WHO/CDS/CSR/ISR/99.4).

Appendix C:

For the subjects who participate only in the first year of efficacy follow-up (until age 12 months), the intended study duration, ***per subject,*** will be approximately 10 months. ***For the subset of subjects who participate in a second year of efficacy follow-up (until age 18 - 24 months), the intended duration of the study, per subject, will be approximately 16 - 22 months.***

Appendix F:

Additional testing for other pathogens is done on rotavirus positive GE stool samples ***during the first year of efficacy follow-up, but not during the second year of efficacy follow-up***, as described in section 5.5.2.

Informed consent/ Subject information sheet (Appendix N):

ONLY FOR STUDY PARTICIPANTS WHO WILL BE FOLLOWED FOR EFFICACY FOR A SECOND YEAR ***UNTIL 18-24 MONTHS*** OF AGE

As your child has not yet completed the follow-up visit at approximately one year of age, we propose to follow him/her for a second year (until age ***18-24*** months). About 1000 children are expected to participate in the second year follow-up.

Interval between visit at 1 year old and visit at approximately ~~**2 years old**~~ ***18 – 24 months*** old.

You will continue the efficacy follow-up during the interval between follow-up visit at one year of age and follow-up visit at ***18-24 months*** ~~two years~~ of age.

Follow-up visit at approximately ~~**2 years**~~ ***18 – 24*** **of age** ***(Brazil and Venezuela: 2 years of age) (Mexico: June 1-> 30, 2003 after the end of RV season)***

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

We will test the stool samples for rotavirus ~~and some other pathogens~~.

Annex 1: Standard Verbal Autopsy Questionnaire (Provided as a separate pdf document) (amended: 26 March 2003)

Approved by: CDM/D title	[redacted]	dd-mm-yyyy
Associate Director, Biometrics	[redacted]	dd-mm-yyyy
Principal Investigator	Dr. [redacted]	dd-mm-yyyy
Principal Investigator	Dr. [redacted]	dd-mm-yyyy
Principal Investigator	Dra. [redacted] M.D.	dd-mm-yyyy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium
Protocol Amendment Approval
Rota-006
444563/006

Protocol Title: A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Amendment 7
Date 21 August 2003

Coordinating Author: [redacted] Scientific Writer

Rationale/background for changes: This amendment was done to allow study end in October 2003 by terminating the second year follow-up of subjects in Brazil and Venezuela.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

The following items in strikethrough or bold italics were amended on 21 August 2003:

Synopsis (Rationale) and Section 1.1:
Efficacy during a second ~~year of~~ efficacy follow-up period will be evaluated in a subset of children (about 1000).

Synopsis (Secondary Objectives) and Section 2.2:
*Second ~~year~~ follow-up **period** (for a subset of about 1000 subjects)*

- To evaluate the efficacy of the HRV vaccine during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period, and during the period starting from 2 weeks after the last HRV/placebo dose until the end of the second efficacy follow-up period.

  The endpoints evaluated for this second ***follow-up period*** analysis (severity and nature of disease, study groups and subsets) will be similar to those evaluated during the first year of follow-up (refer to section 10.5.4 for details).

Synopsis (Study Design) and Section 3:
- All subjects will be followed for efficacy until one year of age and a subset, about 1000 subjects, will be followed for efficacy until ***a maximum of*** two years of age.
- For the subset of subjects who participate in ~~a~~ ***the*** second ~~year of~~ efficacy follow-up ***period*** (until ***maximum*** age ~~18 –~~ 24 months), the intended duration of the study, per subject, will be ~~approximately 16 –~~22 months ***at most***.

Synopsis (Study Participation) and Section 3:
Study visit at the end of the second ~~year of~~ efficacy follow-up ***period*** (~~approximately 18 –~~ 24 months of age **maximum**) – Efficacy Follow-up. This will be the final study visit for the subjects who participate in a second ~~year of~~ efficacy follow-up ***period***.

Synopsis (Secondary Endpoints) and Section 10.2:
For the subset of subjects who participate in a second ~~year of~~ efficacy follow-up

period (until ***maximum*** age ~~18~~ – 24 months):

Definitions and Section 10.2:
Second ~~year of~~ efficacy follow-up ***period****:* Approximately 1000 subject will be followed for a second efficacy analysis either until ~~the age of two years~~ ***October 2003*** (for subjects from Brazil and Venezuela) or until the end of the 2003 rotavirus season (for subjects from Mexico).

Section 5.2:
For the subjects who participate in ~~a~~ ***the*** second ~~year of~~ efficacy follow-up ***period***, the follow-up visit at the end of the second efficacy follow-up period (at ***maximum*** 24 months of age) will be the final visit.

Section 5.3:
§For subjects who participate in a second ~~year of~~ efficacy follow-up ***period***

Size of interval (First efficacy follow-up visit → Second efficacy follow-up visit)
Brazil and Venezuela: ~~335–395 days~~ ***until 01 -> 31 October 2003***

Section 5.4:
Second efficacy follow-up visit: Efficacy Follow-up
Maximum ~~18~~ – 24 months of age (Brazil and Venezuela: ~~335–395 days~~ ***until 01 -> 31 October 2003***)

These subjects will be followed until 2 years of age **maximum** (all of them), thus the final visit will be at end of second efficacy follow-up (**maximum** 24 months of age).

- Study Conclusion for the subjects who participate in the second ~~year of~~ efficacy follow-up ***period***.

Section 5.5.2:
Also, stool samples will be collected during each episode of gastroenteritis which occur from the first dose until **study end** ~~2 years of age~~. During the second ~~year of~~ efficacy follow-up ***period***, the stool samples will be tested only for rotavirus, there will be no local testing for the presence of enteric pathogens.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Section 6.4:
All subjects who have not completed the follow-up visit at 1 year of age as of October 31, 2002, will have an extended follow-up for rotavirus gastroenteritis ~~for one more year~~ with an additional follow-up visit at approximately 18 - 24 months of age.

Appendix C:

- For the subjects who participate only in the first year of efficacy follow-up (until age 12 months), the intended duration of the study, per subject, will be approximately 10 months for subjects. For the subset of subjects who participate in a second ~~year of~~ efficacy follow-up ***period*** (until ***maximum*** age ~~18 –~~ 24 months), the intended duration of the study, per subject, will be ~~approximately 16 –~~ 22 months ***at most***.

Appendix F:
Additional testing for other pathogens is done on rotavirus positive GE stool samples during the first year of efficacy follow-up, but not during the second ~~year of~~ efficacy follow-up ***period***, as described in section 5.5.2.

Appendix N:
Follow-up visit at ~~approximately~~ maximum ~~18 –~~ 24 of age (Brazil and Venezuela: ~~2 years of age~~ *until 01 -> 31 October 2003*) (Mexico: June 1-> 30, 2003 after the end of RV season)

Approved by:

Clinical Development Manager	[redacted]	dd-mm-yyyy
Associate Director, Biometrics	[redacted]	dd-mm-yyyy
Principal Investigator	Dr. [redacted]	dd-mm-yyyy
Principal Investigator	Dr. [redacted]	dd-mm-yyyy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Principal Investigator	Dra. [redacted] M.D.	dd-mm-yyyy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Annex 2

Standard Verbal Autopsy Questionnaire

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

Protocol Investigator Agreement

File note

By Central Study Coordinator: [redacted]
Date: 02 NOV 2004

Identification of the Protocol / amendment version: Rota-006 (444563/006)

I hereby confirm for the Amendments 1-7, Site Specific Amendment and Modification of Rota-006, investigators signature refer to the version indicated in the footer.

[redacted]
CSC [redacted]

SmithKline Beecham Brasil
Av. Comandante Guaranys, 447
Jacarepagua, Rio de Janeiro
Brasil 22775-610

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{6.1}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.
Medical Monitor (Brasil)	[redacted] M.D. Av. Comandante Guaranys, 447 Jacarepagua, Rio de Janeiro Brasil 22775-610 Tel: [redacted] Fax: [redacted]
Clinical Study Director	[redacted] M.D. Av. Comandante Guaranys, 447 Jacarepagua, Rio de Janeiro Brasil 22775-610 Tel: [redacted] Fax: [redacted]

This protocol was developed based upon Version 11.2 of SmithKline Beecham Biologicals' Standard Protocol Template.

(Principal) Investigators

Dr. [redacted]

Brasil

Dra. [redacted]

Brazil

[redacted]

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the clinical study as described and will adhere to the Ethical and Regulatory Considerations stated. I have read and understood the contents of the Investigator Brochure.

[redacted] 31-10-2000

Signat[redacted] Date

(Principal) Investigator name

SmithKline Beecham Brasil
Av. Comandante Guaranys, 447
Jacarepagua, Rio de Janeiro
Brasil 22775-610

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{6.1}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.
Medical Monitor (Mexico)	[redacted] M.D. SmithKline Beecham Mexico, Av. Insurgentes Sur 1605 piso 20, Colonia San Jose Insurgentes Mexico D.F. CP04800 Tel: [redacted] Fax: [redacted]
Clinical Study Director	[redacted] M.D. Av. Comandante Guaranys, 447 Jacarepagua, Rio de Janeiro Brasil 22775-610 Tel: [redacted] Fax: [redacted]

SmithKline Beecham Brasil
Av. Comandante Guaranys, 447
Jacarepagua, Rio de Janeiro
Brasil 22775-610

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{6.1}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.
Medical Monitor (Venezuela)	[redacted] MD SmithKline Beecham, Avenida El Dorado No 91 - 50 Tel: [redacted] or [redacted] Fax: [redacted]
Clinical Study Director	[redacted] M.D. Av. Comandante Guaranys, 447 Jacarepagua, Rio de Janeiro Brasil 22775-610 Tel: [redacted] Fax: [redacted]

(Principal) Investigator Dra. [redacted]

Venezuela

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the clinical study as described and will adhere to the Ethical and Regulatory Considerations stated. I have read and understood the contents of the Investigator Brochure.

[redacted] 14-11-2000

Signature [redacted] Date

(Principal) Investigator name

Appendix K: Protocol Amendments/Modifications

Amendment 1

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{\mathbf{5.8}}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Rationale of the amendment:

The target concentration of one of the clinical lots to be used in this clinical study is $10^{6.1}$ ffu. The actual release titer of the lot DRVC004A46 to be used in the proposed trial is $10^{5.8.}$ ffu . The variability of the titration test which is performed for routine vaccine lot releaseis 0.3 logs. The clinical lot $10^{5.8}$ ffu is in the range of the targeted dose. The following changes were also implemented: to direct parents to contact study personnel for every case of gastroenteritis, to define the immunogenicity and stool subset, delete gastroenteritis stool testing for cryptosporidia; and to clarify the use of several lots for the commercial vaccines.

The following strikethrough and bolded italic text were amended:

Throughout the protocol including Study Title, Synopsis, Section 1.2 – Rationale, Section 2, Section 3 – Study design, Section 6.1.1 – SmithKline Beecham Biologicals' HRV vaccine, Appendix H, all references to viral concentration $10^{6.1}$ ffu were changed to $10^{5.8}$ ffu.

Cover Page

SmithKline Beecham *Mexico*
Av. Insurgentes Sur 1605 piso 20
Colonia San Jose Insurgentes
Mexico D.F.CP04800

SmithKline Beecham *Colombia*
Avenida El Dorado No 91 - 50
Bogota, Colombia

Medical Monitor (Venezuela)

[redacted] MD
SmithKline Beecham ***Costa Rica***
300 m Este de la Escuela La Betania
Carretera Sabanilla
Apdo 10196 – 1000
San Jose, Costa Rica
Tel: [redacted]
Fax: [redacted]

SYNOPSIS

Rationale

The main objective of this study is to evaluate the efficacy of the study vaccine to prevent any rotavirus gastroenteritis. This study will also contribute to dose selection ***and assess the immune response to concomitantly administered routine vaccinations (DTPw-HB+Hib vaccine*).**

Objectives

Primary

- For ***a range of*** viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' HRV vaccine, to demonstrate the efficacy of two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations in preventing any rotavirus gastroenteritis* during the period starting from 2 weeks after dose 2 until the end of the efficacy follow-up period.

Secondary

Efficacy

- For ***a range of*** viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' HRV vaccine, to assess if two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations can:
- ***Prevent rotavirus gastroenteritis due to virus types heterologous to vaccine strain.***

Immunogenicity

- To assess vaccine take, in subjects previously uninfected with rotavirus before vaccination, two months after each study vaccine dose ***in a subset of*** 800 subjects ~~enrolled~~.
- To explore ***in a subset of*** 800 subjects the effect of SB Biologicals' rotavirus vaccine on the immune response to concurrently administered routine vaccinations.
- To assess viral shedding in the vaccine groups ***in a subset***.

Note: the immunogenicity/stool subset is described in section 6.4.

Study design

Study Procedures

Visit 2 (4 Months of Age) – Blood sample in a subset (~~the first~~ 800 subjects ~~enrolled~~), Dose 2 of study vaccine or placebo and Dose 2 of routine vaccinations (DTPw-HB+Hib vaccine).

Visit 3 (6 Months of Age) – Blood sample in a subset (~~the first~~ 800 subjects ~~enrolled~~) and Dose 3 of routine vaccinations (DTPw-HB+Hib vaccine).

- Stool samples will be collected from ~~the first~~ ***a subset of*** 400 subjects enrolled on the day of administration of dose 1 and dose 2 and on day 7 following each dose of study vaccine.
- For each suspected gastroenteritis episode occurring from day of dose 1 until study end, ***a stool sample will be collected*** as soon as possible after the onset of gastroenteritis ***and will be brought as soon as possible to the study site.*** A second stool specimen will be collected ~~by the Health Worker~~ if the first stool sample was not sufficient.

Secondary endpoints

Efficacy

- ***Occurrence of rotavirus gastroenteritis due to virus types heterologous to vaccine strain during the period starting from two weeks after dose 2 until the end of the efficacy follow-up period.***

Immunogenicity endpoints

Two months after dose 2 (at Visit 3) and at year 1 (at Visit 4) in a subset (~~the first~~ 800 subjects ~~enrolled~~).

Analyses The final analysis will be performed at the end of the efficacy follow-up period, after all enrolled subjects have completed visit 4. An interim analysis will be performed on immunogenicity and reactogenicity of the vaccines ***to provide early information on dose selection of phase III studies.*** The interim results will be limited to summaries by group.

2.1 Primary objective

- For ***a range of*** viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{\mathbf{5.8}}$ ffu) of SB Biologicals' HRV vaccine, to demonstrate the efficacy of two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations in preventing any-rotavirus gastroenteritis* during the period starting from 2 weeks after dose 2 until the end of the efficacy follow-up period.

2.2 Secondary objectives

Efficacy

For ***a range of*** viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{\mathbf{5.8}}$ ffu) of SB Biologicals' HRV vaccine, to assess if two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations can:

- ***Prevent rotavirus gastroenteritis due to virus types heterologous to vaccine strain.***

Immunogenicity

- To assess vaccine take, in subjects previously uninfected with rotavirus before vaccination, two months after each study vaccine dose ***in a subset of*** 800 subjects ~~enrolled~~…
- To explore ***in a subset of*** 800 subjects the effect of SB Biologicals' rotavirus vaccine on the immune response to concurrently administered routine vaccinations.
- To assess viral shedding in the vaccine groups ***in a subset***.

Note: the immunogenicity/stool subset is described in section 6.4.

3. Study Design Overview

Visit 2 (4 Months of Age) – Blood sample in a subset (~~the first~~ 800 subjects ~~enrolled~~), Dose 2 of study vaccine or placebo and Dose 2 of routine vaccinations (DTPw-HB+Hib vaccine).

Visit 3 (6 Months of Age) – Blood sample in a subset (~~the first~~ 800 subjects ~~enrolled~~) and Dose 3 of routine vaccinations (DTPw-HB+Hib vaccine).

An interim analysis will be performed on immunogenicity and reactogenicity of the vaccines ***to provide early information on dose selection of phase III studies.***

- Stool samples will be collected from ~~the first~~ ***a subset of*** 400 subjects enrolled on the day of administration of dose 1 and dose 2 and on day 7 following each dose of study vaccine.

- For each suspected gastroenteritis episode occurring from day of dose 1 until study end, ***a stool sample will be collected*** as soon as possible after the onset of gastroenteritis ***and will be brought as soon as possible to the study site.*** A second stool specimen will be collected ~~by the Health Worker~~ if the first stool sample was not sufficient.

4.3 Exclusion criteria

- Acute disease at time of enrollment. (Acute disease is defined as the presence of moderate or severe illness with ***or without*** fever i.e. temperature ≥ 37.5°C as measured by an axillary thermometer or ≥ 38.0°C as measured by a rectal thermometer). A temperature greater than or equal to these cut-off warrants deferral of the vaccination pending recovery of the subject.

5.2 General study aspects

Each study site will receive a "Road book" providing guidelines for the conduct of the study.

Surveillance of gastroenteritis and collection of stool samples

An active surveillance for gastroenteritis ~~efficacy~~ will be conducted via weekly visits to a subject by study personnel (Health Worker) starting 1 week after dose 1 and ending at Visit 4. There ***need*** be no weekly follow-up in weeks when a study clinic visit is scheduled. ~~For each subject, assuming enrollment at 8 weeks of age and completion at 52 weeks of age, there will be 41 weekly home visits.~~ The weekly follow-up by a Health Worker may be done at the subject's home, at a

health clinic, or other mutually convenient place. At weekly follow-up, Health Workers will inquire about the occurrence of gastroenteritis and serious adverse events (disabling illness, hospitalization, death). In cases of gastroenteritis, ***parents should contact the study site personnel***…

~~Subjects enrolled in this study will be followed from the day of first vaccination until 1 year of age for the occurrence of gastroenteritis. For each gastroenteritis episode, 1 stool sample should be collected. A second stool sample will be collected on a different day if the first stool sample was insufficient.~~

Parents/guardians should use the containers… The parents/guardians/***health worker*** should write the date of collection on the container/ziplock bag label with a black ink or ballpoint pen.

5.3 Outline of study procedures

Age	**2 months**	**4 months**	**6 months**	**1 year**
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2** ***MO 4***	**Post vacc 2** **MO *10***
Randomisation	•			
Recording of ***solicited symptoms,*** non serious adverse events within 42 days after dose 1 and dose 2, by investigator		•	•	
Contact (field visit) every week ~~to check on the occurrence of any serious AE or gastroenteritis episodes~~	◊	◊	◊	◊
Return of ***GE*** diary ~~cards~~	•	•	•	•
GE diary ~~card~~ transcription		•	•	•

~~The double-line border following Visit 3 aims to distinguish the data that will be included in the analyses of immunogenicity/safety on all available data around June 30, 2001~~.

5.4 Detailed description of study stages/visits

Visit 1: Dose 1	**6 to 12 weeks (42 to 90 days) of age**

- ***Randomisation (or subject) number attribution.***

- Collection of a stool sample at the day of or 1 day prior to vaccination from ~~the first~~ ***a subset of*** 400 subjects enrolled, to determine the presence of rotavirus.

Interval between Visit 1 and 2

Day 0 to Day 14 (At bedtime):

- The following data will be recorded ~~by the parent/guardian~~ on the diary-card:

Day 7 ± 1:

- ***Collection of a stool sample in a subset (400 subjects).***

Any time between Visit 1 and Visit 2

- Recording ~~by the parent/guardian~~ of unsolicited symptoms, including any SAE.

- Diary cards will also be provided to the parents/guardians of all subjects to daily record the following information until symptoms resolve during each suspected episode of gastroenteritis occurring between visits: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. ~~Parent/guardians will be asked to record whether~~ ***R***ehydration or other medication ***will be recorded***.

Visit 2: Vaccine dose 2 4 Months of Age (49 to 83 days after 1st vaccination)

- Collection of blood sample in a subset (~~first~~ 800 subjects~~ enrolled at Visit 1~~) for serology: a minimum of 1 ml of whole blood to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.
- Collection of a stool sample at the day of or 1 day prior to vaccination from a subset (~~first~~ 400 subjects~~ enrolled at Visit 1~~) to determine the presence of rotavirus.

Interval between Visit 2 and 3

Day 0 to Day 14 (At bedtime):

- The following data will be recorded ~~by the parent/guardian~~ on the diary card:

Day 7 ± 1:

- ***Collection of a stool sample in a subset (400 subjects).***

Any time between Visit 2 and Visit 3

- Recording ~~by the parent/guardian~~ of unsolicited symptoms, including any SAE.

- Diary cards will also be provided to the parents/guardians of all subjects to daily record the following information until symptoms resolve during each suspected episode of gastroenteritis occurring between visits: axillary/rectal

temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. ~~Parent/guardians will be asked to record whether~~ ***R***ehydration or other medication ***will be recorded***.

Visit 3: Dose 3 of routine vaccines and Follow-up	**6 Months of Age (49 to 83 days after 2nd vaccination)**

- Collection of blood sample in a subset (~~first~~ 800 subjects~~ enrolled at Visit 1~~) for serology: a minimum of 3 mls of whole blood to provide a minimum of 1.5 mls of serum according to instructions in Appendix D.

Interval between Visit 3 and Visit 4

Continued efficacy follow-up:

- A Health Worker will visit the parent/guardian weekly (except for weeks when a study clinic visit is scheduled) to assess the completion or collection of diary card information, check on the occurrence of ~~any adverse event, including any~~ SAE or gastroenteritis episodes and if appropriate, collect stool samples.
- Diary cards will also be provided to the parents/guardians of all subjects to daily record the following information until symptoms resolve during each suspected episode of gastroenteritis occurring between visits: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. ~~Parent/guardians will be asked to record whether~~ ***R***ehydration or other medication ***will be recorded***.

Visit 4: Efficacy Follow-up	**1 Year of Age (160 - 200 days after Visit 3)**

- Collection of blood sample from subjects for serology: a minimum of 3 mls of whole blood for the subjects in the subset (~~first~~ 800 subjects~~ enrolled at Visit 1~~) and a minimum of 1 ml in all other subjects.
- Document the administration of routine EPI vaccines ***in the interval before Visit 4; there is no requirement to document vaccines administered at Visit 4***.

5.5.2 Laboratory assays

Stool Analysis

Stool samples will be collected from ~~the first~~ ***a subset of*** 400 subjects enrolled, on the day of or 1 day prior to administration of dose 1 and dose 2 and on day 7 following each dose… If rotavirus is detected (by rapid rotavirus detection kit) in the stool sample, part of the stool sample should be analysed locally for culture of enteric pathogens ~~including~~ ***such as*** Salmonella, Shigella, and Campylobacter. ETEC and ***EPEC*** ~~cryptosporidiosis~~ will be determined ~~by PCR~~ at a central laboratory. The other part of the stool sample will be sent to core laboratory ***A*** to be tested by ELISA to confirm the presence of rotavirus. The other part of the stool sample will be sent to core laboratory***(ies)*** ~~B~~ to be tested by ELISA to confirm the presence of rotavirus. ***Diagnosis of rotavirus gastroenteritis will be by ELISA***…

Any additional testing on stools will be performed if deemed necessary by SmithKline Beecham Biologicals if any findings in the present study or in other studies necessitate investigation of the immunogenicity of the vaccine.

Immunogenicity

For the ***immunogenicity subset (N=800)*** ~~first 800 subjects enrolled~~, a minimum of 1 ml of whole blood will be collected at Visits 1 and 2 and a minimum of 3 mls of whole blood will be collected at Visits 3 and 4, using tubes with serum separator.

Antigen	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off	Core Laboratory
rotavirus	ELISA	in-house	U/ml	20	**TBD***
anti-PRP	ELISA	in-house	mcg/ml	0.15	***TBD***
anti-D	ELISA	in-house	IU/ml	0.1	***TBD***
anti-T	ELISA	in-house	IU/ml	0.1	***TBD***
anti-BPT	ELISA	in-house	EL.U/ml	15	***TBD***
anti-HBs	ELISA	in-house	mcg/ml	10	***TBD***
anti-polio 1	micro-neutralization test	in-house	-	8	***TBD***
anti-polio 2	micro-neutralization test	in-house	-	8	***TBD***
anti-polio 3	micro-neutralization test	in-house	-	8	***TBD***

5.5.3 Serology plan

Study Group	Blood sampling timepoint			Antigen	No. subjects
	Timing	**Month**	**Visit no.**		
A, B & C	Pre	0	1	rotavirus only	2640
A, B & C	Post I	2	2	rotavirus only	800
A, B & C	Post II ***MO 4***	4	3	all	800
A, B, C & D	Post II MO ***10***	10	4	all rotavirus only	800 1840

6.1.4 Commercial EPI vaccines

Vaccine	Lot no.	Formulation One dose (0.5ml) of vaccine contains	Presentation
DTPw-HB+Hib vaccine	~~One~~ Commercial ***Lots*** will be used	Each 0.5 mL dose contains: Whole cell pertussis ≥ 4 IU Diphtheria toxoid ≥ 30 IU (25 Lf); Tetanus toxoid ≥ 60 IU (10 Lf); HBsAg 10 mcg; PRP 10 mcg bound to 30 mcg tetanus toxoid; 2-phenoxyethanol, polysorbate 20, Sodium chloride, thiomersal, lactose, water for injection	DTPw-HB+Hib vaccine is presented as 2 individual components. DTPw-HB vaccine ~~as a turbid white suspension in a monodose vial~~ and Hib vaccine ~~as a white pellet in a glass vial.~~
Polio Sabin	~~One~~ Commercial ***Lots*** will be used	Poliovirus type 1 (LS-c, 2ab) 10^6 $TCID_{50}$; Poliovirus type 2 (P712, Ch, 2ab) 10^5 $TCID_{50}$; Poliovirus type 3 (Leon $12a_1b$) $10^{5.5}$ $TCID_{50}$; Magnesium chloride; Neomycin	Liquid~~: multi-dose vials Ready for use.~~

6.4 Treatment allocation and randomisation

Randomisation of supplies

To allow SmithKline Beecham to take advantage of greater rates of recruitment than anticipated at individual centres in this multicentre study, and to thus reduce the overall study recruitment period, a 10% over-randomisation of supplies will be prepared~~ to provide 2904 vaccine numbers~~.

Randomisation of subjects

The randomisation will be performed using a central randomisation system on Internet. The randomisation algorithm uses a minimisation procedure stratified by centre [23]. ***All countries/centers must use internet randomization, however in case of unexpected technical problems, the classical randomization will be done.***

For centres using the Internet randomisation, **w**hen a subject is eligible and the parent/guardian has given informed consent, the person who is in charge of the vaccination will access the randomisation system on Internet. Upon providing the subject initials and birth date, the randomisation system will determine the vaccine number to be used for the subject. ***For centres using the classical randomisation, subjects will be administered the vaccine dose with the lowest number still available at the study centre.*** The vaccine number will also be used as patient identification number (PID) for all data collected on the subject under the study.

The first 200 (100) subjects enrolled in each country will provide a blood (stool) sample. The remaining subset of 200 (100) blood (stool) samples will come indifferently from any of the participating countries, according to the order of enrollment. In all, the subset that provides additional blood samples will contain 800 subjects and the subset that provides stool samples on day 0 and day 7 will contain 400 subjects.

8.1 Eliciting and documenting adverse events

Recording adverse events

In case a subject is diagnosed with intussusception immediate reporting to the sponsor will be mandatory. Refer to section 8.5. The diagnosis of intussusception should be documented ***by*** radiography…

8.5.2 Reporting serious adverse events

Study Contact for Reporting Serious Adverse Events	
Brazil *Medical Monitor:* [redacted] MD Tel: [redacted] ***Cell:*** [redacted]	*Clinical Research Associate:* [redacted] Tel: [redacted] *Clinical Research Associate:* [redacted] CP04800 Tel: [redacted] Cell: [redacted]
Venezuela *Medical Monitor:* [redacted] MD SmithKline Beecham ***Costa Rica*** ***300 m Este de la Escuela La Betania*** ***Carretera Sabanilla*** ***Apdo 10196 – 1000*** ***San Jose, Costa Rica*** Tel: [redacted] Fax: [redacted]	*Clinical Research Associate:* [redacted] SmithKline Beecham, ***Colombia*** *Avenida El Dorado No 91 - 50* ***Bogota, Colombia*** Tel: [redacted] Fax: [redacted]
Back-up Study Contact for Reporting Serious Adverse Events	
Venezuela: [redacted] ***SmithKline Beecham Venezuela*** ***Calle La Guarita, Edificio Los Frailes, Piso 3, Chuao, Caracas*** ***Tel:*** [redacted] ***Fax:*** [redacted]	

10.2 Secondary endpoints

Efficacy endpoints

- ***Occurrence of rotavirus gastroenteritis due to virus types heterologous to vaccine strain during the period starting from two weeks after dose 2 until the end of the efficacy follow-up period.***

Immunogenicity endpoints

Two months after dose 2 (at Visit 3) and at year 1 (at Visit 4) in a subset (~~the first~~ 800 subjects ~~enrolled~~).

10.3 Study cohorts/data sets to be evaluated

ATP cohort for analysis of immunogenicity

For inclusion in the ATP cohort for immunogenicity, intervals between visits 1 and 2 and between visits 2 and 3 need to be at least 49 days and must not exceed 83 days.

10.4 Estimated sample size

The primary objective is to demonstrate that, for ***a range of*** viral concentration ($10^{4.7}$-ffu, $10^{5.2}$ ffu and $10^{\mathbf{5.8}}$ ffu) of SB Biologicals' HRV vaccine, two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations can prevent rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the efficacy follow-up period following vaccination.

The analysis will consist in looking at the pooled vaccine groups versus placebo and each vaccine group versus placebo.

In order to control the risk of falsely concluding below 5%, the primary objective will be addressed using a hierarchical testing. ***Pooled vaccine groups will be first tested and, only if efficacy has been demonstrated, will t***he vaccine with a viral concentration of $10^{\mathbf{5.8}}$ ffu ***be tested***. ***Likewise, only if efficacy of vaccine with a viral concentration of $10^{5.8}$ ffu has been demonstrated,*** will the vaccine with a viral concentration of $10^{5.2}$ ffu be tested...

The target sample size is 2640 enrolled subjects to reach 2360 subjects in the ATP cohort of efficacy (590 in each group). Table 10.4.1 indicates the level of accuracy that can be expected for the evaluation of efficacy ***for a vaccine group*** to any rotavirus gastroenteritis (primary objective) and to severe rotavirus gastroenteritis (secondary objective) with this sample size. ***Power is higher for the evaluation of efficacy on pooled vaccine groups.***

10.5 Final analyses

The final analysis will be performed at the end of the efficacy follow-up period, after all enrolled subjects have completed visit 4. An interim analysis will be

performed on immunogenicity and reactogenicity of the vaccines ***to provide early information on dose selection.*** The interim results will be limited to summaries by group.

10.5.4 Efficacy analysis

The vaccine efficacy rate (VE), expressed as 100% X (1-Relative Risk), will be calculated ***for pooled vaccine groups and for each vaccine group,*** with their 95% CI (see Appendix J for mathematical detail) against:

- ***rotavirus gastroenteritis due to virus types heterologous to vaccine strain.***

The primary objective is to demonstrate that ***pooled HRV vaccine groups can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the efficacy follow-up period, and subsequently that*** the HRV vaccine with a viral concentration of $10^{5.8}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the efficacy follow-up period, and subsequently that the HRV vaccine with a viral concentration of $10^{5.2}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the efficacy follow-up period, and subsequently that the HRV vaccine with a viral concentration of $10^{4.7}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the efficacy follow-up period.

The efficacy of the pooled vaccine groups will be first evaluated. If the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the efficacy follow-up period following vaccination in the pooled HRV groups is statistically significantly lower than in the placebo group (two-sided Fisher Exact test : $p < 0.05$), one will conclude that the efficacy of the pooled HRV vaccine groups in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the efficacy follow-up period has been demonstrated.

If in addition the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the efficacy follow-up period following vaccination in the HRV group with a viral concentration of $10^{5.8}$ ffu is statistically significantly lower than in the placebo group (two-sided Fisher Exact test : $p < 0.05$), one will conclude that the efficacy of the HRV vaccine with a viral concentration of $10^{5.8}$ ffu in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the efficacy follow-up period has also been demonstrated.

And, if in addition the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2…

10.6 Interim analysis

An interim analysis will be performed ***to provide early information on dose selection***…

Appendix C: Overview of the recruitment plan

- Target enrollment will be 2640 subjects (approximately ***1020 in Brazil***; 800 in Mexico and 820 in Venezuela).

- ~~Enrollment will start around January 15, 2001.~~

Appendix D: Handling of Biological Samples Collected by the Investigator

4. Sorting and storage

The tubes of serum should be stored in a vertical position at a temperature between -20°C and -70°C until shipment to core laborator***y*** (ies) ~~A and/or B~~. Wherever possible, a backup facility for storage of serum samples should be available.

Instructions for Handling of Stool Samples

The stool specimens will be processed by the investigator's laboratory into stool suspensions and then stored at a temperature between -20°C and -70°C until shipment to core laboratory***(ies)*** ~~B~~.

Appendix E: Shipment of Biological Samples

The investigator will coordinate the shipment of samples to ~~core laboratory B (SB Biologicals in Rixensart, Belgium or to Dr.~~ [redacted] ~~laboratory in Cincinnati, OH.) and/or~~ a core laboratory to be determined.

Appendix F: Laboratory Assays

1.2.2 *Antigen Detection in GE Stool Samples*

A rapid screening will be performed at the study sites to determine the presence of rotavirus in the stool using a commercial test (Rotaclone or equivalent).

Additional testing for other pathogens is done on rotavirus positive GE stool samples, as described in section 5.5.2.

Appendix H: Sample Subject Information and Informed Consent

2. Description/Purpose of the Study

This is a medical research study... We will look for side effects (like fever, ***loss of appetite,*** fussiness/***irritability***, vomiting, diarrhea ***[three or more looser than normal stools within a day]*** and runny nose/cough).

We will test the human rotavirus vaccine at 3 different strengths. Various strengths of the investigational rotavirus vaccine have been tested already in ***more than*** 200 infants and previously an earlier version of the vaccine made by another manufacturer was tested in approximately 200 infants.

After your child is vaccinated, we will see whether the human rotavirus vaccine prevents any and severe rotavirus gastroenteritis. We will diagnose rotavirus gastroenteritis by collecting stool samples from infants that develop gastroenteritis (diarrhea). We will test the stool samples for rotavirus ***and some other pathogens.***

4. Study Participation and Study Procedures

Also at that appointment, study personnel will ask you questions about your child's medical history and medicines that your child may be taking. For ~~the first~~ ***a subset of*** 400 subjects enrolled, we will collect a stool sample on the day of vaccination. We will collect a stool sample on the day of vaccination…

Visit 1 (2 months of age):

- You will be asked questions about your child's health, your child will be examined by the doctor and his/her temperature will be taken. You will be asked to provide a stool sample ***if your child is one of 400 infants selected for stool tests. This stool sample will be tested for rotavirus.***
- Randomisation will be performed after the blood draw.
- If your child ***is*** one of 400 ***infants selected for stool tests***, you will be asked to collect a stool sample 7 days after vaccination.
- For each episode of gastroenteritis, ***you*** will be instructed ***to contact the study site personnel and*** to daily record the following on a diary card until

symptoms resolve: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. You will be asked to collect one stool sample. A second stool sample will be collected ~~by the Health Worker~~ on a different day if the first sample was insufficient.

Visit 2 (4 months of age):

- If your child ***is*** one of 400 ***infants selected for stool tests***, you will be asked to collect a stool sample on the day of vaccination.
- If your child is ***one of*** 800 ***infants selected for blood tests of the vaccine***, a blood sample (1ml) will be collected ~~from your child to test the effectiveness of the vaccine~~.
- If your child ***is*** one of 400 ***infants selected for stool tests***, you will be asked to collect a stool sample 7 days after vaccination.
- For each episode of gastroenteritis, ***you*** will be instructed ***to contact the study site personnel and*** to daily record the following on a diary card until symptoms resolve: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. You will be asked to collect one stool sample. second stool sample will be collected ~~by the Health Worker~~ on a different day if the first sample was insufficient.

Visit 3 (6 months of age):

- If your child is ***one of*** 800 ***infants selected for blood tests*** a blood sample (3mls) will be collected ~~from your child~~ to test the effectiveness of the investigational vaccine and the routine pediatric vaccines.
- For each episode of gastroenteritis, ***you*** will be instructed ***to contact the study site personnel and*** to daily record the following on a diary card until symptoms resolve: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. You will be asked to collect one stool sample. A second stool sample will be collected ~~by the Health Worker on a different day~~ if the first sample was insufficient.

Visit 4 (1 year of age):

- If your child is ***one of*** 800 ***infants selected for blood tests***, a blood sample (3mls) will be collected ~~from your child~~ to test the effectiveness of the investigational vaccine and the routine pediatric vaccines. For all other children, a 1 ml blood sample will be taken from your child to determine the effectiveness of the ***investigational*** vaccine ***only***.

- ~~For each episode of gastroenteritis, parents/guardians will be instructed to daily record the following on a diary card until symptoms resolve: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. You will be asked to collect one stool sample. A second stool sample will be collected by the Health Worker on a different day if the first sample was insufficient.~~

The quantity of the stool sample should be at minimum 2 spoons (the spoon is within the stool container) and at maximum half of the container. Write the name, date of collection on the container label with a black ballpoint pen~~ and store the container in the freezer, screw cap facing upwards~~. A field worker will collect the stool samples.

4. Potential Risks Associated with the Study

There are risks if your child enters this study. The risks come from the use of an investigational human rotavirus vaccine and from collection of ***a maximum of 4*** blood samples. These risks are explained below.

The human rotavirus vaccine may cause allergic reactions… Your child must stay in your doctor's office for 30 minutes after each ***study*** vaccine dose so that any reaction can be treated.

The human rotavirus vaccine given to your child… ***If your child is one of 800 infants selected for blood tests***, we will test your child's blood for antibody levels expected from the routine vaccines at 6 and 12 months of age…

If your child is ***one of 800 infants selected for blood tests***, a 1 ml blood sample will be taken at Visits 1 and 2 and a 3 ml blood sample will be taken at Visits 3 and 4…

Your child will receive routine vaccinations recommended by the EPI. These vaccines may cause side effects including pain and swelling at the injection site, high fever, fussiness/irritability, vomiting, and poor feeding***, and in very rare cases allergic reactions.***

Appendix I: Follow-up of intussusception cases

2. Data collection for intussusception cases

The investigator will document all available information regarding any intussusception cases occurring during the clinical studies on the Serious Adverse Event pages ~~contained in the individual eCRF~~ and fax within 24 hours (1 calendar

day) of his/her becoming aware of the event to the SmithKline Beecham Contact for Serious Adverse Event (SAE) Reporting.

To allow for a complete assessment of the intussusception cases, information on the subject's feeding practices, immunization history, as well as any other information thought necessary for assessment by the study staff should be reported to the SB safety contact ***by using the IS reporting form***.

3. Serum, throat and stool specimen collection from intussusception cases

If possible a stool specimen should be collected… The hospital microbiology laboratory should divide each stool specimen into an aliquot for its own testing and two additional aliquots of at least 2 grams each to be frozen at ***–20°C to*** –70°C... One swab specimen should be submitted for bacterial culture and the other 2 swabs should be placed each in a separate tube of 2 ml of sterile virus transport media and frozen at ***–20°C to*** –70°C.

A throat swab should be collected as soon as possible after intussusception is diagnosed. The throat swab should be placed in 2 ml of sterile virus transport media and frozen at ***–20°C to*** –70°C.

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 6, 2001
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. **(amended: 06-FEB-2001)**

Approved by: Director	[redacted]	12.02.2001 dd-mm-yy
Group Director	[redacted]	dd-mm-yy
Head Biometrican		12/2/2001 dd-mm-yy
Investigators	Dr [redacted]	dd-mm-yy
	Dr. [redacted]	dd-mm-yy
	Dra [redacted]	dd-mm-yy
	Dra [redacted]	dd-mm-yy

Approved by:

Director	[redacted]	dd-mm-yy
Group Director	[redacted]	8 Feb 01 dd-mm-yy
Head Biometrican	[redacted]	dd-mm-yy
Investigators	Dr[redacted]	dd-mm-yy
	Dr[redacted]	dd-mm-yy
	Dra[redacted]	dd-mm-yy
	Dra[redacted]	dd-mm-yy

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. **(amended: 12-FEB-2001)**

Approved by:		
Director	[redacted]	dd-mm-yy
Group Director	[redacted]	dd-mm-yy
Head Biometrican	[redacted]	dd-mm-yy
Investigators	[redacted]	19 March 2001 dd-mm-yy
	Dr [redacted]	dd-mm-yy
	Dr [redacted]	dd-mm-yy
	Dra. [redacted]	dd-mm-yy

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. **(amended: 12-FEB-2001)**

Approved by:

Director	[redacted]	dd-mm-yy
Group Director	[redacted]	dd-mm-yy
Head Biometrican	[redacted]	dd-mm-yy
Investigators	Dr. [redacted]	dd-mm-yy
	[redacted]	26/02/01
	Dr. [redacted]	dd-mm-yy
	Dra [redacted]	dd-mm-yy
	Dra [redacted]	dd-mm-yy

Rota-006: File note

Confusion concerning date for Amendment 1

Final correct date is 12 Feb 2001.
Confusion comes from the fact that very minor changes have been done by Rixensart between 06 Feb 2001 and 12 Feb 2001.
Final version dated 12 Feb (with correction of the date of amendment) has been sent by [redacted] on the 12 Feb 2001 but in the meantime local CRAs were already in possession of versions still indicating 06 Feb by error.

[redacted] 17/10/2003

FILE NOTE:

By Central Study Coordinator: [redacted]
Date: 04 NOV 2003.

Signature Page ROTA-006:

I hereby confirm for the Final Protocol of study 444563/006 dated 20 October 2000, and for Amendment 1, dated February 6, 2001, the Signature pages were not signed by Investigator **Dra.** [redacted]

Reason: There are no documents about signature and approval from this investigator as her center participation has been canceled.

[redacted]
CSC

[redacted]

Modification 1

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Rationale of the modification:

This protocol was modified to change the principal investigator and medical monitor in Venezuela, to delete a principal investigator in Brasil, to change the clinical research associate in Brasil and to delete [redacted] as the back-up contact for reporting serious adverse events.

The following strikethrough and bolded italic text were amended:

Cover Page

(Principal) Investigators	~~Dra.~~ [redacted] ~~Brasil~~ [redacted]
Medical Monitor (Venezuela)	***Dr.*** [redacted] SmithKline Beecham ***Venezuela*** ***Calle La Guarita Edf. Los Frailes. Piso 3*** ***Chuao / Caracas*** ***Venezuela*** Tel: [redacted] ***Mobile:*** [redacted]
(Principal) Investigator	***Dra.*** [redacted] ***M.D.*** [redacted] ***Venezuela***

8.5.2 Reporting serious adverse events

Study Contact for Reporting Serious Adverse Events	
Brazil	*Clinical Research Associate:* [redacted] SmithKline Beecham Brasil, Av. Comandante Guaranys, 447 Jacarepagua, Rio de Janeiro Brazil 22775-610 Tel: [redacted] or [redacted] Fax: [redacted]
Venezuela *Medical Monitor:* ***Dr.*** [redacted] SmithKline Beecham ***Venezuela*** ***Calle La Guarita Edf. Los Frailes.*** ***Piso 3*** ***Chuao / Caracas*** ***Venezuela*** Tel: [redacted] ***Mobile*:** [redacted]	
Back-up Study Contact for Reporting Serious Adverse Events	
~~Venezuela:~~ [redacted] ~~SmithKline Beecham Venezuela~~ ~~Calle La Guarita, Edificio Los Frailes, Piso 3, Chuao, Caracas~~ ~~Tel:~~ [redacted] ~~Fax:~~ [redacted]	

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	**May 14, 2001**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by: Clinical Development Manager	[redacted]	15.05.2001 dd-mm-yy
Investigators	Dr [redacted]	dd-mm-yy
	Dr. [redacted]	dd-mm-yy
	Dra [redacted]	dd-mm-yy

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	**May 14, 2001**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by:
Clinical Development Manager

[redacted] dd-mm-yy

Investigators

[redacted] 24 May 2001
dd-mm-yy

Dr [redacted] dd-mm-yy

Dra [redacted] dd-mm-yy

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	**May 14, 2001**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by: Clinical Development Manager	[redacted]	15.05.2001 dd-mm-yy
Investigators	Dr [redacted]	dd-mm-yy
	Dr [redacted]	dd-mm-yy
	[redacted]	04.06.2001 dd-mm-yy

Site-specific Amendment

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.
Date	October 10, 2001 – Site-specific amendment

Rationale of the amendment:

Natural rotavirus infection is known to afford clinical protection against subsequent episodes of disease and specific IgA in serum and in fecal samples are considered to be good predictors of protection against natural rotavirus illness.

Fecal rotavirus IgA immune response and the role of IgA antibodies as marker of protection against rotavirus disease will be therefore evaluated in a site-specific study in Venezuela. A subset of 200 infants from Venezuela enrolled in study rota-006 and receiving GSK Biologicals' HRV vaccine or placebo will participate in this site-specific study.

The following bolded italic text were amended:

Synopsis

Study design **Study Procedures**

- ***As part of a site-specific sub-study in Venezuela, stool samples, up to a maximum of 10 over the study period, will be collected from a subset of 200 subjects enrolled in Venezuela. Also, two additional stool samples will be collected from this subset during each gastroenteritis episode occurring during the study period.***

3. Study Design Overview

- ***As part of a site-specific sub-study in Venezuela, stool samples, up to a maximum of 10 over the study period, will be collected from a subset of 200 subjects enrolled in Venezuela. Also, two additional stool samples will be***

collected from this subset during each gastroenteritis episode occurring during the study period.

5.4 Detailed description of study stages/visits

Please refer to Appendix L for information on additional stool sampling for the subset of 200 subjects participating in the site-specific study in Venezuela.

5.5.2 Laboratory assays

Stool Analysis

Please refer to Appendix L for information on laboratory assays to be performed on additional stool samples collected from the subset of 200 subjects participating in the site-specific study in Venezuela.

10.5.3 Analysis of immunogenicity
Please refer to Appendix L for information on analysis and reporting of results on stool analysis from the subset of 200 subjects participating in the site-specific study in Venezuela.

Appendix H: Sample Subject Information and Informed Consent

4. Study Participation and Study Procedures

If you live in Venezuela, you may be asked to collect 10 additional stool samples from your child for further testing of your child's response to the vaccine. This additional testing will be performed in 200 infants.

Visit 1 (2 months of age):

- ***If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect a stool sample just before vaccination and 14 and 28 days after vaccination. This stool sample will be used for further testing of your child's response to the vaccine.***

- ***If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect two additional stool samples for each episode of gastroenteritis: one at 1-5 days after onset of symptoms and the second at 14 days after onset of symptoms.***

Visit 2 (4 months of age):

- ***If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect a stool sample just before vaccination and 14 and 28 days after vaccination. This stool sample will be used for further testing of your child's response to the vaccine.***

- ***If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect two additional stool samples for each episode of gastroenteritis: one at 1-5 days after onset of symptoms and the second at 14 days after onset of symptoms.***

Visit 3 (6 months of age):

- ***If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect a stool sample every two months from six months of age until Visit 4.***

- ***If your child is one of 200 infants selected for stool tests in Venezuela, you will be asked to collect two additional stool samples for each episode of gastroenteritis: one at 1-5 days after onset of symptoms and the second at 14 days after onset of symptoms.***

Appendix L: Site-specific study of rotavirus specific IgA antibodies in feces in Venezuela

Appendix L, with details regarding the site-specific study in Venezuela, was added to the protocol.

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by: Director	[redacted]	11/10/2001 dd-mm-yy
Head Biometrican	[redacted]	12/10/2001 dd-mm-yy
Investigators	Dr[redacted]	dd-mm-yy

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by:

Director [redacted] dd-mm-yy

Head Biometrican [redacted] dd-mm-yy

Investigator [redacted] 05 - 11 - 2001
Dra [redacted] dd-mm-yy

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	**May 14, 2001**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by:
Clinical Development Manager

[redacted] dd-mm-yy

Investigators

Dr [redacted] dd-mm-yy

Dr [redacted] dd-mm-yy

D [redacted] 05 - 11 - 2001 dd-mm-yy

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. **(amended: 12-FEB-2001)**

Approved by:

Director [redacted] dd-mm-yy

Group Director [redacted] dd-mm-yy

Head Biometrican [redacted] dd-mm-yy

Investigators

Dr [redacted] dd-mm-yy

Dr [redacted] dd-mm-yy

01-11-01

Dra [redacted] dd-mm-yy

Dra [redacted] dd-mm-yy

Modification: May 14, 2001
Site-specific amendment: October 10, 2001

FILE NOTE:

By Central Study Coordinator [redacted]
Date: 17 NOV 2003.

Signature Page Site Specific Amendment ROTA-006:

I hereby confirm for the Site **Specific Amendment** of study 444563/006 dated 10 October 2001, the Signature page was not signed by Dr [redacted]

Reason: This Site Specific Amendment was not for Brazil so is not relevant to be signed in that country.

[redacted]

CSC [redacted]

File note for Rota-006 study

By Central Study Coordinator: [redacted]
Date: 18 NOV 2004

Signature of the Site specific Amendment by Dr [redacted]
Dr [redacted] was not Principal Investigator anymore at the time of the Site Specific Amendment however, she was still involved in the study. As she signed the Site specific amendment, we keep the signed page in the file but it was not requested to obtain this signature

[redacted]
CSC [redacted]

Amendment 2

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Rationale of the amendment:

This amendment will allow termination of enrolment in Mexico by end December 2001 to avoid vaccinating subjects during the rotavirus season. Indeed, rotavirus infection either prior to vaccination or during the vaccination period is an elimination criterion from the primary efficacy analysis and if enrolment was continued during the season, a large proportion of infants enrolled during this period would then have to be eliminated. On the other hand, there is no rotavirus season as such in Venezuela and Brazil and enrolment of eligible subjects will continue in these two countries with the aim to compensate the lower recruitment in Mexico.

The addresses of the GSK offices in Brazil and Mexico have been modified.

The following strikethrough and bolded italic text were amended:

Cover Page
~~Av. Comandante Guaranys, 447~~
~~Jacarepagua, Rio de Janeiro~~
~~Brasil 22775-610~~
GlaxoSmithKline
Diretoria Médica - Pesquisa Clinica - II Andar
Estrada Dos Bandeirantes, 8464
Jacarepagua
CEP: 22783-110
Rio de Janeiro, Brazil

~~Av. Insurgentes Sur 1605 piso 20,~~
~~Colonia San Jose Insurgentes~~
~~Mexico D.F.~~
~~CP04800~~
Calzada Mexico Xochimilco N° 4900
1er piso
Colonia San Lorenzo Huipulco
Delegacion Tlalpan
CP 14370, Mexico D.F.

Medical Monitor (Brazil)

[redacted] M.D.
~~Av. Comandante Guaranys, 447~~
~~Jacarepagua, Rio de Janeiro~~
~~Brasil 22775-610~~
~~Tel:~~ [redacted]
~~Fax:~~ [redacted]
GlaxoSmithKline
Diretoria Médica - Pesquisa Clinica - II Andar
Estrada Dos Bandeirantes, 8464
Jacarepagua
CEP: 22783-110
Rio de Janeiro, Brazil
Tel: [redacted]
Fax: [redacted]

Medical Monitor (Mexico)	[redacted] M.D. ~~Av. Insurgentes Sur 1605 piso 20,~~ ~~Colonia San Jose Insurgentes~~ ~~Mexico D.F.~~ ~~CP04800~~ ~~Tel:~~ [redacted] ~~Fax:~~ [redacted] ***Calzada Mexico Xochimilco N° 4900*** ***1er piso*** ***Colonia San Lorenzo Huipulco*** ***Delegacion Tlalpan*** ***CP 14370, Mexico D.F.*** ***Tel:*** [redacted] ***Fax:*** [redacted]
Clinical Study Director	[redacted] M.D. ~~Av. Comandante Guaranys, 447~~ ~~Jacarepagua, Rio de Janeiro~~ ~~Brasil 22775-610~~ ~~Tel: 55 21 44 40 355~~ ~~Fax: 55 21 44 54 331~~ ***GlaxoSmithKline*** ***Diretoria Médica - Pesquisa Clinica - II Andar*** ***Estrada Dos Bandeirantes, 8464*** ***Jacarepagua*** ***CEP: 22783-110*** ***Rio de Janeiro, Brazil*** ***Tel:*** [redacted] ***Fax:*** [redacted]

<u>Section 6.4</u>

Randomisation of supplies

The enrolment in Mexico will be terminated by end December 2001 to avoid vaccinating subjects during the rotavirus season. Thus, no further subjects will be enrolled in Mexico after December 31, 2001. Enrolment of eligible subjects will continue in Venezuela and Brazil to compensate the lower recruitment in Mexico.

Section 8.5.2

Study Contact for Reporting Serious Adverse Events	
Brazil *Medical Monitor:* [redacted] MD ~~Av. Comandante Guaranys, 447~~ ~~Jacarepagua, Rio de Janeiro~~ ~~Brasil 22775-610~~ ~~Tel:~~ [redacted] ~~Fax:~~ [redacted] ***GlaxoSmithKline*** ***Diretoria Médica - Pesquisa Clinica - II Andar*** ***Estrada Dos Bandeirantes, 8464*** ***Jacarepagua*** ***CEP: 22783-110*** ***Rio de Janeiro, Brazil*** Tel: [redacted] Fax: [redacted]	Clinical Research Associate: [redacted] ~~Av. Comandante Guaranys, 447~~ ~~Jacarepagua, Rio de Janeiro~~ ~~Brasil 22775-610~~ ~~Tel:~~ [redacted] ~~or~~ [redacted] ~~Fax:~~ [redacted] ***GlaxoSmithKline*** ***Diretoria Médica - Pesquisa Clinica - II Andar*** ***Estrada Dos Bandeirantes, 8464*** ***Jacarepagua*** ***CEP: 22783-110*** ***Rio de Janeiro, Brazil*** Tel: [redacted] Fax: [redacted]
Mexico *Medical Monitor:* Dr. [redacted] ~~Av. Insurgentes Sur 1605 piso 20,~~ ~~Colonia San Jose Insurgentes~~ ~~Mexico D.F.~~ ~~CP04800~~ ~~Tel:~~ [redacted] ~~Fax:~~ [redacted] ***Calzada Mexico Xochimilco N° 4900*** ***1er piso*** ***Colonia San Lorenzo Huipulco*** ***Delegacion Tlalpan*** ***CP 14370, Mexico D.F*** Tel: [redacted] Fax: [redacted]	*Clinical Research Associate:* [redacted] ~~Av. Insurgentes Sur 1605 piso 20,~~ ~~Colonia San Jose Insurgentes~~ ~~Mexico D.F.~~ ~~CP04800~~ ~~Fax: 525 480 31 18~~ ***Calzada Mexico Xochimilco N° 4900*** ***1er piso*** ***Colonia San Lorenzo Huipulco*** ***Delegacion Tlalpan*** ***CP 14370, Mexico D.F*** Fax: [redacted]

Appendix C

- ***. The enrolment in Mexico will be terminated by end December 2001 to avoid vaccinating subjects during the rotavirus season. Thus, no further subjects will be enrolled in Mexico after December 31, 2001. Enrolment of***

eligible subjects will continue in Venezuela and Brazil to compensate the lower recruitment in Mexico.

- Target enrollment will be 2640 subjects ~~(approximately 1020 in Brazil; 800 in Mexico and 820 in Venezuela)~~.

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 1	December 11, 2001
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.6}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by:		
Director	[redacted]	12 Dec 2001 dd-mm-yy
Head Biometrician	[redacted]	12/12/2001 dd-mm-yy
Investigators	Dr [redacted]	dd-mm-yy
	Dr [redacted]	dd-mm-yy
	Dra [redacted]	18.12.2001 dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment ~~1~~ 2	December 11, 2001
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by: Director	[redacted]	dd-mm-yy
Head Biometrician	[redacted]	dd-mm-yy
Investigators	Dr [redacted]	30 January 2002 dd-mm-yy
	Dr [redacted]	dd-mm-yy
	Dr [redacted]	dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by:		
Director	[redacted]	dd-mm-yy
Head Biometrician	[redacted]	dd-mm-yy
Investigators	[redacted]	dd-mm-yy
	[redacted]	15/01/02 dd-mm-yy
	Dra [redacted]	dd-mm-yy

Amendment 3

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Rationale of the amendment:

This protocol was amended on **May 3, 2002** for the following major items:

- The results of an interim analysis of immunogenicity have shown that the immune response to the HRV vaccine after a two-dose regimen was lower than that observed previously in clinical studies conducted with this vaccine in Europe. The relevance of this lower response in terms of efficacy is unknown, since no serological correlates of protection are defined for rotavirus disease.

  The purpose of this amendment is to allow administration of a third dose of the HRV vaccine to a subset of 200 infants in order to assess whether a three-dose schedule can lead to a higher immune response. A blood sample will be drawn from this subset at two months after the second and the third dose of study vaccine or placebo.

- To decrease the sample size because of difficulty in enrolling eligible subjects for participation in the study. The new sample size will allow evaluation of the study objectives.

  The assessment of efficacy in protecting from rotavirus disease will be performed as planned originally in a cohort of about 2000 children who have received two doses of the HRV vaccine.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002

The following strikethrough and bolded italic text were amended:

Synopsis (indication)

A subset of subjects (N = 200) will receive a third dose of the HRV vaccine at 6 months of age.

Synopsis (rationale) and Section 1.2

A third dose of the HRV vaccine will be administered to a sub-group of 200 infants in order to explore whether a 3-dose schedule can lead to a higher immune response.

Synopsis (primary objective) and Section 2.1

For the subset of subjects who receive two doses of HRV or placebo (N=2076)

Synopsis (secondary objectives) and Section 2.2

Efficacy

For the subset of subjects who receive two doses of HRV or placebo (N=2076):

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' …….

For the subset of subjects who receive three doses of HRV or placebo (N=200):

- ***To explore the rates of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end the efficacy follow-up period.***

Immunogenicity

For the subset of subjects who receive two doses of HRV or placebo (N=2076):

- To assess persistence of serum IgA to rotavirus at ~~Visit 4~~ ***the final visit.***

For the subset of subjects who receive three doses of HRV or placebo (N=200):

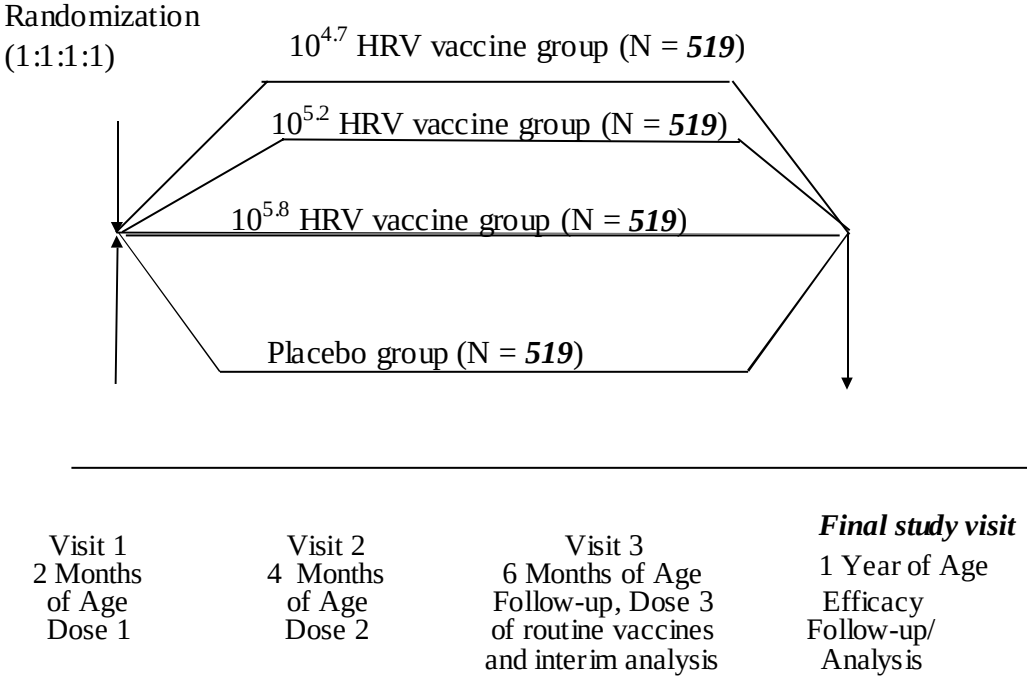
- ***To assess serum IgA to rotavirus, two months after dose 2 and dose 3 of study vaccine or placebo.***
- ***To assess viral shedding in the vaccine groups after the third HRV vaccine dose.***
- ***To explore the effect of SB Biologicals' rotavirus vaccine on the immune response to concurrently administered routine vaccinations two months after the third dose of routine vaccines.***

Safety/Reactogenicity

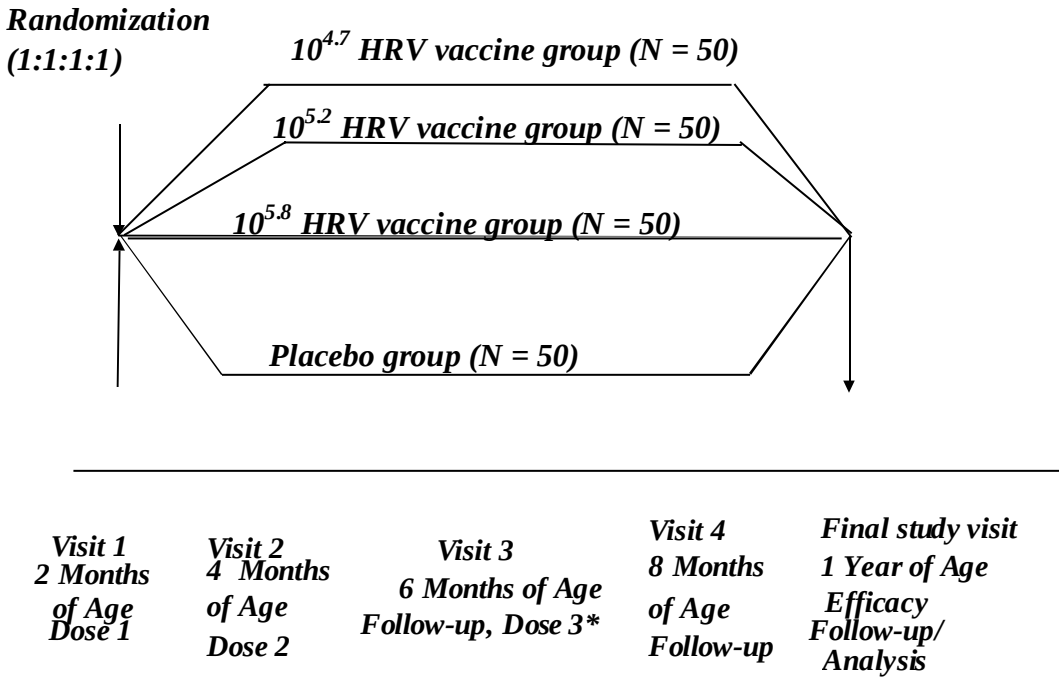
- ***To assess the safety and reactogenicity of the third dose of SB Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo in a subset of subjects (N=200).***

<u>Section 3</u>

For the subset of subjects who receive two doses of HRV or placebo:



For the subset of subjects who receive three doses of HRV or placebo:



HRV vaccine/placebo and routine vaccines

<u>Synopsis (study design) and Section 3</u>

- Indication:

  A subset of subjects (N = 200) will receive a third dose of the HRV vaccine at 6 months of age.
- Blinding: double-blind for HRV vaccine and placebo. The parents/guardians of the subjects and the study personnel will be blinded to the treatment administered. Blinding will be maintained for the whole study period (up to ***the final study visit*** that will take place approximately 10 months after study start). Refer to section 6.5.

Study Procedures

Final study visit (1 Year of Age) – Blood sample from subjects ***who receive two doses of study vaccine or placebo***, and Efficacy Follow-up.

A subset of subjects (N = 200) enrolled in Brazil and Venezuela will receive a third dose of the HRV vaccine or placebo along with blood sampling at Visit 3. A study visit (Visit 4) will take place for these subjects two months after the third dose of study vaccine or placebo to collect a blood sample and the final

study visit will take place at approximately one year of age. A blood sample will not be taken from this subset at the final visit. These subjects will have 5 study visits in total.

- Active follow-up for safety and gastroenteritis via weekly visit to a subject by study personnel (Health Worker) starting 1 week after dose 1 and ending at ***the final study visit***.
- 15-day follow-up period (day 0 to day 14) on solicited symptoms (fever, fussiness / irritability, diarrhea, vomiting, loss of appetite and cough/runny nose) after any dose of study vaccine using diary cards ***(in a subset of 200 subjects after dose 3).***
- Blood samples will be drawn from all subjects at study Visits 1, ***from subjects receiving two doses of study vaccine or placebo at the final visit*** and in a subset (N = 800) at Visits 2 and 3. ***Blood samples will be drawn from the subset receiving three doses of study vaccine or placebo (N = 200) at Visit 3 (two months after dose 2) and Visit 4 (two months after dose 3).***
- ***Stool samples will be collected from the subset receiving three doses of study vaccine/placebo (N = 200) on the day of administration of dose 3 and on day 7 following dose 3 of study vaccine.***
- Recording of unsolicited symptoms within 42 days after dose 1, dose 2 ***(in all subjects)***, ***and dose 3 (in a subset of 200 subjects)*** of the study vaccines.
- If any G1 rotavirus is detected in the stool specimens between Visit 1 and Visit 3 ***(Visit 4 for the subset receiving three doses of study vaccine or placebo)***, vaccine virus will be …….

Synopsis (number of subjects) and Section 4.1

Target enrollment ~~will be~~ ***was planned at*** 2640 (660 subjects in each group) to obtain 2360 evaluable subjects (590 each group) for the analysis of the primary objective.

However, the target sample could not be reached because of difficulty in enrolling eligible subjects for participation in the study. The final enrollment is of 2276 eligible subjects.

Synopsis (analyses)

The final analysis will be performed at the end of the efficacy follow-up period, after all enrolled subjects have completed ~~visit 4~~ ***the final study visit***. ***Two*** ~~An~~ interim analyses will be performed on immunogenicity …….

Section 4.4

4.4 Elimination criteria during the study up to Visit 3 ***(up to Visit 4 for the subset of 200 subjects receiving three doses of study vaccine/placebo)***

These elimination criteria should be also checked on the day of dose 3 of study vaccine/placebo in the subset of 200 subjects (at Visit 4 for the subset receiving three doses of study vaccine/placebo).

Section 4.5

4.5 Elimination criteria during the study from Visit 3 ***or Visit 4 (for the subset of 200 subjects receiving three doses of study vaccine/placebo) until the final study visit***

The following criteria should be checked at ***the final study visit for all subjects*** ~~visit 4~~.

Section 5.2

In a subset of 200 subjects the 3d dose of DTPw-HB/Hib will be given concomitantly with the third dose of study vaccine/placebo.

Surveillance of gastroenteritis and collection of stool samples

An active surveillance for gastroenteritis ~~efficacy~~ will be conducted via weekly visits to a subject by study personnel (Health Worker) starting 1 week after dose 1 and ending at ***the final study visit*** ~~Visit 4~~.

Section 5.3

Subjects ~~participating in each part of the study~~ ***who receive two doses of study vaccine*** will have four study visits. ***Subjects who receive three doses of study***

vaccine will have five study visits. The study procedures at each visit are outlined below.

Age	**2 months**	**4 months**	**6 months**	***8 months***	**1 year**
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	***VISIT 4 DOSE 3 SUBSET ONLY****	**~~VISIT 4~~ FINAL VISIT**
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 *MO 4***	***Post vacc 3 MO 6***	**Post vacc 2 MO *10***
Informed consent	•				
Medical history	•				
Check of inclusion criteria	•				
Check of exclusion criteria	•				
Check of elimination criteria		•	•	•	•
Check of contraindications	•	•	•		
Physical examination	•	•	•	•	•
Pre-vaccination body temperature	•	•	•		
Measure/record height and weight	•	•	•	•	•
Blood sampling	• (1 ml of blood)	• (1 ml of blood in a subset#)	• (3 mls of blood in a subset#) ***• (1 ml of blood in dose 3 subset*)***	***• (3 mls of blood in dose 3 subset*)***	• (3 mls of blood in a subset#, 1 ml ***for subjects receiving two doses***)
Randomisation	•				
Stool samples will be collected from a subset (N = 400) on the day of administration of dose 1 and dose 2 and on day 7 following each dose. ***Stool samples will be collected from a subset (N = 200) on the day of administration of dose 3 and on day 7 following dose 3***	•	•	•		
Study Vaccine	•	•	• ***(dose 3 subset*)***		
Routine Vaccination	•	•	•		
Daily post-vaccination recording of solicited symptoms (days 0–14) by parents/guardians	•	•	• ***(dose 3 subset*)***		
Collection of stool samples	•	•	•	• ***(dose 3 subset*)***	•
Recording of solicited symptoms, non serious adverse events within 42 days after dose 1, dose 2 ***and dose 3 (in a subset)***, by investigator		•	•	• ***(dose 3 subset*)***	
Contact (field visit) every week	◊	◊	◊	◊	◊

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002

Age	**2 months**	**4 months**	**6 months**	***8 months***	**1 year**
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	***VISIT 4 DOSE 3 SUBSET ONLY****	**~~VISIT 4~~ FINAL VISIT**
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 *MO 4***	***Post vacc 3 MO 6***	**Post vacc 2 MO *10***
Return of GE diary	•	•	•	• ***(dose 3 subset*)***	•
GE diary transcription		•	•	• ***(dose 3 subset*)***	•
Documentation of routine EPI vaccines	•	•	•	• ***(dose 3 subset*)***	•
Recording medication	•	•	•	• ***(dose 3 subset*)***	
Reporting of Serious Adverse Events occurring throughout the study period	•	•	•	• ***dose 3 (subset*)***	•
Study Conclusion					•

#Subset for immunogenicity evaluation (N = 800)
****Subset receiving three doses of study vaccine/placebo (N = 200)***

Intervals between study visits* ***for subjects receiving 2 doses of study vaccine/placebo will be as follows***

Interval	**Size of interval**
1 (Visit 1→Visit 2)	49 - 83 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→ ~~Visit 4~~ ***Final visit***)	160 - 200 days

*The date of the previous visit is the reference date.

Intervals between study visits* for subjects included in the subset receiving 3 doses of study vaccine/placebo will be as follows

Interval	***Size of interval***
1 (Visit 1→Visit 2)	***49 - 83 days***
2 (Visit 2→Visit 3)	***49 - 83 days***
3 (Visit 3→Visit 4)	***49 – 83 days***
4 (Visit 3→Final visit)	***160 - 200 days***

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002

The date of the previous visit is the reference date.

Section 5.4

Visit 3: Dose 3 of routine vaccines and Follow-up	6 Months of Age (49 to 83 days after 2nd vaccination)

In addition, to the above mentioned study procedure, the following study procedures will be done at Visit 3 for the subset of 200 subjects enrolled in Brazil and Venezuela who receive three doses of study vaccine or placebo:

- ***Collection of blood sample for serology: a minimum of 1 mls of whole blood to provide a minimum of 0.5 mls of serum according to instructions in Appendix D.***
- ***Collection of a stool sample at the day of or 1 day prior to vaccination.***
- ***Administration of study vaccines:***
  - ***Oral administration of third dose of the study vaccine or placebo according to the guidelines set out in Section 6.2. Study vaccine must be given before the routine vaccines. If regurgitation occurs immediately (within 30 minutes) after administration, do not give another dose and record in the eCRF.***
- ***The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.***
- ***At the end of the 30 minutes of observation period, a diary card will be provided to the parents/guardians of the subjects who received the third dose of study vaccine/placebo to record body temperature (measured by a axillary/rectal route), the number of looser than normal stools passed by the subject, the number of vomiting episodes, any loss of appetite, any fussiness/irritability, any cough/runny nose during the 15-day solicited follow-up period, as well as unsolicited symptoms occurring within 42 days after dose 3.***
- ***Recording the subject's feeding schedule for the subset who received the third dose of study vaccine/placebo. The parent/guardian will be questioned whether the child is fed with breast milk or infant formula and whether the child was fed within 60 minutes before vaccination and/or 30 minutes after vaccination.***

NOTE: Subjects receiving 3 doses of study vaccine or placebo will have Visit 4 approximately two months after Visit 3. Final study visit (Visit 5) for these subjects will take place approximately 4 months after.

Interval between Visit 3 and 4 for subjects included in the subset receiving 3 doses of study vaccine/placebo

Day 7 +/-1: collection of a stool sample

Day 0 to Day 14 (At bedtime):

- ***The following data will be recorded on the diary card:***
  - ***general solicited symptoms (fever, irritability/fussiness, diarrhea, vomiting, loss of appetite, cough/runny nose)***
  - ***unsolicited symptoms, including any SAE***

Interval between Visit 3 and ~~Visit 4~~ *final study visit*

Continued efficacy follow-up:

- Parents/guardians of all subjects will be instructed to collect one stool sample if they suspect that the subject has gastroenteritis symptoms (diarrhea) between Visits 3 and ~~4~~ ***final study visit***.

Visit 4 only for subjects receiving 3 doses of study vaccine/placebo: Follow-up	**8 Months of Age (49 to 83 days after Visit 3)**

- ***Physical examination with measurement and recording of height and weight.***
- ***Check elimination criteria.***
- ***Recording previous/concomitant medication (see section 6.9).***
- ***Collection of blood sample for serology: a minimum of 3 mls of whole blood to provide a minimum of 1.5 mls of serum according to instructions in Appendix D.***
- ***Collection and verification of diary card containing information on adverse experiences occurring from Visit 3 until Visit 4. The investigator will verify the diary card(s) and transcribe the information into the appropriate sections of the eCRF, in English. The study monitor may help in this translation. Any unreturned diary cards will be sought through telephone call(s) or any other convenient procedure.***

- ***Recording of unsolicited adverse events that may have occurred on day 0-42 after dose 3.***
- ***Recording of serious adverse events that may have occurred since previous visit.***
- ***The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.***

***Final study visit (Visit 4 for subjects receiving 2 doses of study vaccine/placebo or Visit 5 for subjects receiving 3 doses of study vaccine/placebo)*: Efficacy Follow-up**	**1 Year of Age (160 – 200 days after Visit 3)**

- Collection of blood sample from subjects for serology: a minimum of 3 mls of whole blood for the subjects in the subset (800 subjects) and a minimum of 1 ml in ~~all other~~ subjects ***who received two doses of study vaccine or placebo***.
- Recording of diary card information on gastroenteritis episodes which occurred since ~~Visit 3~~ ***the previous visit***. The investigator will transcribe the information into the appropriate sections of the eCRF.
- Document the administration of routine EPI vaccines in the interval before ***the final visit***; there is no requirement to document vaccines administered at ***the final visit***.

Section 5.5.2

Stool analysis

Stool samples will be also collected from the subset receiving three doses of study vaccine/placebo (N = 200) on the day of or 1 day prior to administration of dose 3 and on day 7 following dose 3 of study vaccine.

Any detection of the vaccine virus in any stool collected after vaccination up to Visit 3 ***(Visit 4 for subset receiving three doses of study vaccine/placebo)*** will be taken ……

…***(Visit 4 for the subset receiving three doses of study vaccine or placebo)***,….

Immunogenicity

For all subjects, a minimum of 1 ml of whole blood will be collected at Visit 1. For subjects receiving two doses of HRV vaccine or placebo, for the immunogenicity subset (N=800), a minimum of 1 ml of whole blood will be collected at Visit ~~1 and~~ 2 and a minimum of 3 mls of whole blood will be collected at Visit 3 and ***at the final study visit***, using tubes with serum separator. For all other subjects ***receiving two doses of vaccine***, a minimum of 1 ml of whole blood will be collected ***at the final study visit***. ***For the subset receiving three doses of study vaccine/placebo (N = 200), a minimum of 1 ml of whole blood will be collected at Visit 3 and a minimum of 3 mls of whole blood will be collected at two months after dose 3 (Visit 4).***

Section 5.5.3

Study Group	**Blood sampling timepoint**			**Antigen**	**No. subjects**
	Timing	**Month**	**Visit no.**		
A, B, C & D	Pre	0	1	rotavirus only	~~2640~~ *2276*
A, B, C & D	Post II MO 4	4	3	all ***rotavirus only***	800 ***200****
A, B, C & D	***Post III MO 6***	***6***	***4***	***all***	***200****
A, B, C & D	Post II MO 10	10	4 ***Final study visit***	all rotavirus only	800 ~~1840~~ ***1276#***

=subset of subjects who receive 3 doses of the study vaccine or placebo
#= only subjects who receive 2 doses of the study vaccine or placebo

Section 6.1.2

~~One lot~~ ***Two lots will be used.***

Section 6.2

Visit	Vaccination	Dose	Vaccine	Route[1]	Site[2]	Side
3 (Subset)	***Rotavirus***	***1***	***Human Rotavirus***	***Oral***	***NA***	***NA***

Section 6.4

The target sample size ~~is~~ ***was planned at*** 2640 enrolled subjects……

A subset of 200 subjects among the last enrolled in Brazil and Venezuela will constitute the subset that will receive three doses of study vaccine/placebo.

Section 6.9

Only at visit 1, 2, 3 ***(for all subjects) and at visit 4 (for the subset receiving three doses of study vaccine/placebo),*** the investigator should question the subject or their legal representative about any medication taken.

Any immunosuppressants or other immune-modifying drugs or treatments administered at ANY time during the period starting 30 days prior to the first dose of study vaccine(s) and ending at Visit 3 ***(Visit 4 for the subset of subjects receiving a third dose of study vaccine/placebo)*** must be …….. Any vaccine other than the study vaccine(s) administered at ANY time during the period starting at birth and ending at ~~Visit 4~~ ***the last study visit*** must be recorded …

Section 8

Surveillance period for occurrence of adverse events

All non-serious adverse events occurring within 42 days after ***each study vaccine/placebo*** dose ~~1 and dose 2~~ must ……

Section 8.5.2

Study Contact for Reporting Serious Adverse Events	
	Clinical Research Associate: [redacted]

	Cell: [redacted]

Section 9.1

From an analysis perspective, any subject who does not come back for ~~Visit 4~~ ***the final study visit*** is a drop-out for the efficacy analysis. A subject who returns for ~~Visit 4~~ ***the final study visit*** is considered to have completed….

Synopsis (primary endpoint) and Section 10.1

For the subset of subjects who receive two doses of HRV or placebo (N=2076).

- Occurrence……..

Synopsis (secondary endpoints) and Section 10.2

Efficacy

For the subset of subjects who receive two doses of HRV or placebo (N=2076)

- Occurrence of ……..

For the subset of subjects who receive three doses of HRV or placebo (N=200):

- ***Occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the efficacy follow-up period.***

Immunogenicity endpoints

For the subset of subjects who receive two doses of HRV or placebo (N=2076).

- Serum rotavirus IgA antibody titers at Visits 1 and ~~4~~ ***the final visit*** and at Visits 2 and 3 in a subset ***(N=800)***.
- Proportion of subjects with vaccine take at visits 2 and 3 in a subset ***(N=800)***.
- Viral shedding in the vaccine groups in a subset ***(N = 400)***.

Two months after dose 2 (at Visit 3) and at year 1 (at ~~Visit 4~~ ***final study visit)*** in a subset (800 subjects).

◊ GMTs for …….

For the subset of subjects who receive three doses of HRV or placebo (N=200):

- ***Serum rotavirus IgA antibody titers at visit 1, 3 and 4.***
- ***GMTs for anti-PRP, anti-diphtheria and anti-tetanus toxoids, anti-BPT, anti-polio types 1, 2 and 3 and anti-HBs two months after dose 3***
- ***Seroprotection status two months after dose 3:***
  - ◊ ***anti-PRP antibody concentrations ≥0.15 and ≥1.0 mcg/ml***
  - ◊ ***anti-diphtheria toxoid antibody concentrations ≥0.1 IU/ml***
  - ◊ ***anti-tetanus toxoid antibody concentrations ≥0.1 IU/ml***
  - ◊ ***anti-HBs antibody concentrations ≥10.0 mcg/ml***
  - ◊ ***anti-polio type 1 antibody titers ≥8***
  - ◊ ***anti-polio type 2 antibody titers ≥8***
  - ◊ ***anti-polio type 3 antibody titers ≥8***
- ***Seropositivity status two months after dose 3:***
  - ◊ ***anti-BPT antibody concentrations ≥15 EL.U/ml***
- ***Viral shedding in the vaccine groups on the day of and on day 7 after dose 3.***

Safety endpoints

- For each type of solicited symptoms, occurrence of the symptom within the 15-day solicited follow-up period after any dose of study vaccine ***(in a subset after dose 3.***
- Occurrence of unsolicited symptoms within 42 days after dose 1, dose 2 ***(in all subjects) and dose 3 (in a subset)***, according to WHO classification.

Section 10.3

The analysis of immunogenicity on the ATP cohorts will be the primary analyses. The analyses of the total cohort for immunogenicity ~~and efficacy~~ will only be performed if more than 5% of the enrolled subjects are excluded from the corresponding ATP cohort. In such case, the total cohort analyses will evaluate whether exclusion from the ATP cohorts could have biased the results.

The ATP efficacy cohort will be used for the primary analysis of efficacy. An analysis of efficacy based on the total cohort will also be performed.

The total cohort will be used for the primary analysis of safety. The analysis on the ATP cohort for safety will only be performed if more than 5% of the enrolled subjects are excluded from the ATP safety cohort.

The analyses of safety, immunogenicity and efficacy for the subset of subjects who received 3 doses of HRV or placebo will be performed on the total cohort.

Section 10.4

The target sample size ~~is~~ ***was*** planned at 2640 enrolled subjects to reach 2360 subjects in the ATP cohort of efficacy (590 in each group). ***However, the target sample size has been reduced because of difficulty in enrolling eligible subjects for participation in the study. In addition, a subset of 200 subjects will receive 3 doses of HRV vaccine or placebo. Target enrollment for subjects who will receive only 2 doses of HRV vaccine or placebo is estimated to be 2076 eligible subjects leaving 460 evaluable subjects per group for the analysis of the primary objective.***

Table 10.4-1 was updated with respect to the actual sample size.

Section 10.5

The final analysis will be performed at the end of the efficacy follow-up period, after all enrolled subjects have completed ~~visit 4~~ ***the final study visit***. ~~An~~ ***Two*** interim analyses will be performed ….

Section 10.5.3

For the subset of subjects who received 2 doses of HRV or placebo:

In addition, for all antigens, the distribution of antibody titers two months after the second dose and at ~~Visit 4~~ ***the final study visit*** will be displayed ……

Difference between each vaccine group and placebo ***two*** months….

For the subset of subjects who received 3 doses of HRV or placebo:

The distribution of antibody titers two months after the second dose (rotavirus only) and after the third dose (all antigens) will be displayed using reverse cumulative curve.

Section 10.5.4

The vaccine efficacy rate (VE) ***for subjects who received 2 doses of HRV vaccine or placebo***, expressed as ……

For the subset of subjects who receive 3 doses of HRV or placebo:

- ***the proportion of subjects reporting any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the***

efficacy follow-up period will be calculated by group and for pooled vaccine groups. An episode of gastroenteritis will be classified positive for rotavirus if the stool samples collected during the episode are positive as tested by Rota Ag ELISA.

Section 10.6

No study report will be written for the interim data and results will be ***strictly controlled*** ~~kept in house~~.

An interim analysis will be performed on post-dose 3 data. This analysis will present a descriptive summary of immunogenicity and reactogenicity for the study vaccine as well as immunogenicity data for routine vaccines. No study report will be written for the interim data and results will be kept in house. Unblinding at the level of individual data will be restricted to the statistician and the database administrator.

The results of interim analyses performed on post-dose 2 and post-dose 3 data may be presented at scientific conferences and, as required, to the authorities.

Appendix C

- Target enrollment ~~will be~~ ***was planned at*** 2640 subjects. ***Final enrolment is 2276 subjects enrolled as follows: 405 in Mexico, 972 in Venezuela and 899 in Brazil***.

Appendix E

Gastroenteritis stool samples have to be sent as infectious substances. Copies of the completed Serum ***and Stool*** Listing Form, and Specimen…..

Appendix G

The following represents the vaccine supplies that will be provided to administer the third dose of study vaccine/placebo to the subset of 200 subjects including 20% over-randomisation:

- ***approximately 60 doses of the $10^{4.7}$ HRV vaccine***
- ***approximately 60 doses of the $10^{5.2}$ HRV vaccine***
- ***approximately 60 doses of the $10^{5.8}$ HRV vaccine***
- ***approximately 60 doses of the placebo***
- ***240 doses of the diluent***

Appendix M

Appendix M was added to the protocol for supplemental subject information and informed consent for study participants who will receive three doses of study vaccine/placebo.

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Date of amendment 3	**May 3, 2002**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by: Director	[redacted]	May 06, 2002 dd-mm-yy
Head Biometrician	[redacted]	May 3, 2002 dd-mm-yy
Investigators	Dr [redacted]	dd-mm-yy
	Dr [redacted]	dd-mm-yy
	Dra [redacted]	dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Date of amendment 3	**May 3, 2002**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by:		
Director	[redacted]	dd-mm-yy
Head Biometrician	[redacted]	dd-mm-yy
Investigators	[redacted]	6 September 2002 dd-mm-yy
	Dr [redacted]	dd-mm-yy
	Dra [redacted]	dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Date of amendment 3	**May 3, 2002**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by:
Director

[redacted] dd-mm-yy

Head Biometrician

[redacted] dd-mm-yy

Investigators

Dr [redacted] dd-mm-yy

[redacted] 20/05/02
dd-mm-yy

Dr [redacted] dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by:		
Director	[redacted]	dd-mm-yy
Head Biometrician	[redacted]	dd-mm-yy
Investigators	Dr [redacted]	dd-mm-yy
	Dr [redacted]	dd-mm-yy
	[redacted] Dra [redacted]	08 MAY 2002 dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002

Amendment 4

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Rationale of the amendment:

This protocol was amended on **July 11, 2002,** to perform an interim analysis in order to provide early information on the efficacy of the HRV vaccine against any and severe rotavirus gastroenteritis in Latin America.

This interim efficacy analysis will not have any impact on the follow-up of subjects nor on the statistical power for the final analysis.

The following strikethrough and bolded italic text were amended:

Synopsis (analyses)

An interim analysis on efficacy against any and severe rotavirus gastroenteritis will be performed to obtain early efficacy data.

The results of ***all*** interim analyses may be presented at scientific conferences and, as required, to the authorities.

Section 10.6

An interim analysis on efficacy against any and severe rotavirus gastroenteritis will be performed to obtain early efficacy data. The interim efficacy analysis will be performed during the efficacy follow-up period, when a number of rotavirus gastroenteritis cases is reached that will allow to demonstrate vaccine efficacy (with LL of 95CI > 0) with 75% power based on the following conservative assumptions: vaccine efficacy (for pooled HRV vaccine groups) against any rotavirus gastroenteritis is 50%, with an attack rate of 6% in the placebo group. No study report will be written for the interim efficacy data and distribution of the results will be strictly controlled. Unblinding at the level of

individual data will be restricted to the statistician and the database administrator.

Table 10.6-1 indicates the level of accuracy that can be expected for the interim evaluation of efficacy against any rotavirus and severe rotavirus gastroenteritis above a specific cut-off.

Table 10.6-1: Power to get an exact 95% CI for the interim vaccine efficacy analysis (pooled vaccine groups versus placebo) above a specific cut-off (460 evaluable subjects per group, power based on 1.000 simulations using Proc StatXact)

% of subjects reporting rotavirus gastroenteritis in the placebo group	*% of subjects reporting rotavirus gastroenteritis in pooled vaccine groups*	*Efficacy (%)*	*Cut-off*
			0%
Any Gastroenteritis			
6%	*1.8%*	*70%*	*97%*
6%	*2.4%*	*60%*	*89%*
6%	*3.0%*	*50%*	*75%*
5%	*1.5%*	*70%*	*96%*
5%	*2.0%*	*60%*	*86%*
5%	*2.5%*	*50%*	*65%*
Severe Gastroenteritis			
3%	*0.9%*	*70%*	*82%*
2%	*0.4%*	*80%*	*79%*
2%	*0.6%*	*70%*	*60%*
2%	*0.8%*	*60%*	*45%*

No adjustment on the alpha or the power will be applied for the final analyses of efficacy.

The results of interim analyses performed on post-dose 2, ***interim efficacy data*** and post-dose 3 data may be presented at scientific conferences and, as required, to the authorities.

Appendix E

~~Gastroenteritis stool samples have to be sent as infectious substances.~~

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Date of amendment 3	May 3, 2002
Date of amendment 4	**July 11, 2002**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002

Approved by: Clinical Development Manager	[redacted]	11/07/02 dd-mm-yy
Head Biometrician	[redacted]	11/7/2002 dd-mm-yy
Investigators	Dr [redacted]	dd-mm-yy
	Dr [redacted]	dd-mm-yy
	Dra [redacted]	dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Date of amendment 3	May 3, 2002
Date of amendment 4	**July 11, 2002**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by: Clinical Development Manager	[redacted]	dd-mm-yy
Head Biometrician	[redacted]	dd-mm-yy
Investigators	[redacted]	6 September 2002 dd-mm-yy
	Dr. [redacted]	dd-mm-yy
	Dr. [redacted]	dd-mm-yy

Approved by:
Clinical Development Manager

[redacted] dd-mm-yy

Head Biometrician

[redacted] dd-mm-yy

Investigators

Dr. [redacted] dd-mm-yy

12-07-02

Dr. [redacted] dd-mm-yy

Dra [redacted] dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002

Approved by:		
Director	[redacted]	dd-mm-yy
Head Biometrician	[redacted]	dd-mm-yy
Investigators	Dr. [redacted]	dd-mm-yy
	Dr. [redacted]	dd-mm-yy
	[redacted] Dra. [redacted]	06 AUG 2002 dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002

Amendment 5

Protocol Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Rationale of the amendment:

This protocol was amended on **September 20, 2002** for the following:

- An interim efficacy analysis has demonstrated the efficacy of the HRV vaccine in preventing rotavirus gastroenteritis in infants after a two-dose regimen.

  The purpose of this amendment is to add a second year of efficacy follow-up (until age 24 months) for the subjects (N = approximately 1000 subjects) who have not completed the study as of October 31, 2002 in order to assess the efficacy during the second efficacy follow-up period.

The following strikethrough and bolded italic text were amended:

Definitions

Efficacy follow-up period: Each subject will be followed for the efficacy analysis starting from two weeks post dose 2 until the age of approximately one year ***(approximately two years for a subset of about 1000 subjects)***.

<u>Section 1.2</u>
Protective efficacy will be evaluated in all enrolled subjects until they reach one year of age. Efficacy during a second year will be evaluated in a subset of children (about 1000).

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002

Synopsis (primary objective) and Section 2.1

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' HRV vaccine, to demonstrate the efficacy of two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations in preventing any rotavirus gastroenteritis* during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period.

Synopsis (secondary objectives) and Section 2.2

Efficacy

First year follow-up

For the subset of subjects who receive two doses of HRV or placebo (N=2076):

- Prevent severe rotavirus gastroenteritis during-the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Prevent rotavirus gastroenteritis due to virus types heterologous to vaccine strain ***from two weeks after dose 2 until the end of the first efficacy follow-up period***. (amended: 12-FEB-2001)
- Prevent any and severe pure rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Prevent mixed rotavirus gastroenteritis (gastroenteritis associated with rotavirus and at least one other pathogen) during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Prevent any hospitalization for rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period (see section 8.5.1 for definition of hospitalization).

For the subset of subjects who receive three doses of HRV or placebo (N~200):

- To explore the rates of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the ***first*** efficacy follow-up period.

Second year follow-up (for a subset of about 1000 subjects)

- ***To evaluate the efficacy of the HRV vaccine during the period starting from the end of the first efficacy follow-up period until the end of the second***

efficacy follow-up period, and during the period starting from 2 weeks after the last HRV/placebo dose until the end of the second efficacy follow-up period.

The endpoints evaluated for this second year analysis (severity and nature of disease, study groups and subsets) will be similar to those evaluated during the first year of follow-up (refer to section 10.5.4 for details).

Immunogenicity

For the subset of subjects who receive two doses of HRV or placebo (N=2076):

- To assess persistence of serum IgA to rotavirus at the ***end of the first efficacy follow-up period*** ~~final visit~~.

Synopsis (analyses)

The final analysis will be performed at the end of the ***first*** efficacy follow-up period, after all enrolled subjects have completed the ***study visit at the end of the first follow-up period***. ***Analysis of data collected during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be presented in an annex.***

Synopsis (study procedures) and Section 3

- ***All subjects will be followed for efficacy until one year of age and a subset, about 1000 subjects, will be followed for efficacy until two years of age.***
- ***For the subjects who participate only in the first year of efficacy follow-up (until age 12 months),*** the intended duration of the study, per subject, will be approximately 10 months for subjects. ***For the subset of subjects who participate in a second year of efficacy follow-up (until age 24 months), the intended duration of the study, per subject, will be approximately 22 months.***

Study Procedures

- Study visits:

Study visit ***at the end of the first efficacy follow-up period*** (1 Year of Age) – Blood sample from subjects who receive two doses of study vaccine or placebo, and Efficacy Follow-up. ***This will be the final study visit for the subjects who participate only in the first year of efficacy follow-up.***

A subset of subjects (N ~ 200) enrolled in Brazil and Venezuela will receive a third dose of the HRV vaccine or placebo along with blood sampling at Visit 3. A study visit (Visit 4) will take place for these subjects two months after the third dose of study vaccine or placebo to collect a blood sample. For these subjects the first ***efficacy follow-up*** study visit will take place at approximately one year of age: a blood sample will not be taken from this subset at ***this visit***. ~~These subjects will have 5 study visits in total.~~.

Study visit at the end of the second efficacy follow-up period (2 Years of Age) – Efficacy Follow-up. This will be the final study visit for the subjects who participate in a second year of efficacy follow-up.

- Active follow-up for safety and gastroenteritis via weekly visit to a subject by study personnel (Health Worker) starting 1 week after dose 1 and ending at the study visit ***at the end of the second efficacy follow-up period***. ***For the subjects who participate only in the first year of efficacy follow-up, active follow-up for safety and gastroenteritis via weekly visit to a subject by study personnel (Health Worker) will end at the study visit at the end of the first efficacy follow-up period.***
- Blood samples will be drawn from all subjects at study Visits 1, from subjects receiving two doses of study vaccine or placebo at the ***end of the first efficacy follow-up period*** ~~final visit~~ and in a subset (N = 800) at Visits 2 and 3. Blood samples will be drawn from the subset receiving three doses of study vaccine or placebo (N ~ 200) at Visit 3 (two months after dose 2) and Visit 4 (two months after dose 3).

<u>Section 4.5</u>

4.5 Elimination criteria during the study from Visit 3 ~~or~~ (*from* Visit 4 ~~(~~for the subset of 200 subjects receiving three doses of study vaccine/placebo) until the ~~final study visit~~ study end

The following criteria should be checked at the ***follow-up visit at the end of the first efficacy follow-up period and at the end of the second efficacy follow-up period as applicable*** ~~final study visit for all subjects~~.

<u>Section 5.2</u>

Surveillance of gastroenteritis and collection of stool samples

For the subjects who participate only in the first year of efficacy follow-up, the follow-up visit at the end of the first efficacy follow-up period (at 1 year of age) will be the final visit. For the subjects who participate in a second year of efficacy follow-up, the follow-up visit at the end of the second efficacy follow-up period (at 24 months of age) will be the final visit.

Section 5.3

All subjects who have not completed the follow-up visit at 1 year of age as of October 31, 2002, will have an additional follow-up visit at approximately 24 months of age. The number of subjects in this case is expected to be about 1000.

Age	**2 months**	**4 months**	**6 months**	**8 months**	***1 year***	***2 years***
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4 DOSE 3 SUBSET ONLY***	***END OF 1ST EFFICACY PERIOD***	***END OF 2ND EFFICACY PERIOD***
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 MO 4**	**Post vacc 3 MO 6**	**Post vacc 2 MO 10**	***Post vacc 2 MO 22***
Informed consent	•					
Medical history	•					
Check of inclusion criteria	•					
Check of exclusion criteria	•					
Check of elimination criteria		•	•	•	•	•
Check of contraindications	•	•	•			
Physical examination	•	•	•	•	•	•
Pre-vaccination body temperature	•	•	•			
Measure/record height and weight	•	•	•	•	•	•
Blood sampling	• (1 ml of blood)	• (1 ml of blood in a subset#)	• (3 mls of blood in a subset#) • (1 ml of blood in dose 3 subset*)	• (3 mls of blood in dose 3 subset*)	• (3 mls of blood in a subset#, 1 ml for subjects receiving two doses)	
Randomisation	•					
Stool samples will be collected from a subset (N = 400) on the day of administration of dose 1 and dose 2 and on day 7 following each dose. Stool samples will be collected from a subset (N ~ 200) on the day of administration of dose 3 and on day 7 following dose 3	•	•	•			
Study Vaccine	•	•	• (dose 3 subset*)			
Routine Vaccination	•	•	•			
Daily post-vaccination recording of solicited symptoms (days 0–14) by parents/guardians	•	•	• (dose 3 subset*)			
Collection of stool samples ***if the child is suspected to have gastroenteritis***	•	•	•	•	•	•
Recording of solicited symptoms, non serious adverse events within 42 days after dose 1, dose 2 and dose 3 (in a subset), by investigator		•	•	• (dose 3 subset*)		

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002

Age	**2 months**	**4 months**	**6 months**	**8 months**	***1 year***	***2 years***
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4 DOSE 3 SUBSET ONLY***	***END OF 1ST EFFICACY PERIOD***	***END OF 2ND EFFICACY PERIOD***
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 MO 4**	**Post vacc 3 MO 6**	**Post vacc 2 MO 10**	***Post vacc 2 MO 22***
Contact (field visit) every week	◊	◊	◊	◊	◊	◊
Return of GE diary	•	•	•	• (dose 3 subset*)	•	•
GE diary transcription		•	•	• (dose 3 subset*)	•	•
Documentation of routine EPI vaccines	•	•	•	• (dose 3 subset*)	•	•
Recording medication	•	•	•	• (dose 3 subset*)		
Reporting of Serious Adverse Events occurring throughout the study period	•	•	•	• dose 3 (subset*)	•	•
Study Conclusion					•¶	•§

#Subset for immunogenicity evaluation (N = 800)
*Subset receiving three doses of study vaccine/placebo (N = 200)
◊ is used to indicate a study procedure which does not require documentation in the individual eCRFs.
¶For subjects who participate only in the first year of efficacy follow-up
§For subjects who participate in a second year of efficacy follow-up

Interval	**Size of interval**
1 (Visit 1→Visit 2)	49 - 83 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→ ***First efficacy follow-up visit***)	160 - 200 days
4 (First efficacy follow-up visit → Second efficacy follow-up visit)	***335–395 days***

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002

*The date of the previous visit is the reference date.

Interval	Size of interval
1 (Visit 1→Visit 2)	49 - 83 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→Visit 4)	49 – 83 days
4 (Visit 3→ ***First efficacy follow-up visit***)	160 - 200 days
5 (First efficacy follow-up visit → Second efficacy follow-up visit)	***335–395 days***

*The date of the previous visit is the reference date.

Section 5.4

Visit 3: Dose 3 of routine vaccines and Follow-up	**6 Months of Age (49 to 83 days after 2nd vaccination)**

These subjects will be followed until 2 years of age (all of them), thus the final visit will be at end of second efficacy follow-up (24 months of age). ~~Final study visit (Visit 5) for these subjects will take place approximately 4 months after.~~

Interval between Visit 3 and *end of the first efficacy follow-up period*

***First efficacy follow-up visit* (Visit 4 for subjects receiving 2 doses of study vaccine/placebo or Visit 5 for subjects receiving 3 doses of study vaccine/placebo): Efficacy Follow-up**	**1 Year of Age (160 – 200 days after Visit 3)**

- Document the administration of routine EPI vaccines since the previous visit ~~in the interval before the final visit; there is no requirement to document vaccines administered at the final visit~~.
- Study Conclusion ***for the subjects who participate only in the first year of efficacy follow-up***.

Interval between end of the first efficacy follow-up period* and *end of the second

efficacy follow-up period visits

Continued efficacy follow-up:

- ***A Health Worker will visit the parent/guardian weekly (except for weeks when a study clinic visit is scheduled) to assess the completion or collection of diary card information, check on the occurrence of SAE or gastroenteritis episodes and if appropriate, collect stool samples.***
- ***Parents/guardians of all subjects will be instructed to collect one stool sample if they suspect that the subject has gastroenteritis symptoms (diarrhea). A second stool sample will be collected on a different day if the first stool sample was insufficient. Two occurrences of gastroenteritis symptoms should be classified as separate episodes if there are 5 or more symptom-free days between the episodes. The study personnel may organise transportation of the stool samples.***
- ***Diary cards will also be provided to the parents/guardians of all subjects to daily record the following information until symptoms resolve during each suspected episode of gastroenteritis occurring between visits: axillary/rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. Rehydration or other medication will be recorded.***

Second efficacy follow-up visit: Efficacy Follow-up	***2 Year of Age (335–395 days after first efficacy follow-up visit)***

- ***Physical examination with measurement and recording of height and weight.***
- ***Check elimination criteria.***
- ***Recording of diary card information on gastroenteritis episodes which occurred since the previous visit. The investigator will transcribe the information into the appropriate sections of the eCRF.***
- ***Recording of serious adverse events that may have occurred since previous visit.***
- ***Document the administration of routine EPI vaccines since the previous visit.***

- ***Study Conclusion for the subjects who participate in the second year of efficacy follow-up.***

Section 5.2

Stool Analysis

Also, stool samples will be collected during each episode of gastroenteritis which occur from the first dose until ***2*** years of age.

Immunogenicity

For subjects receiving two doses of HRV vaccine or placebo, for the immunogenicity subset (N=800), a minimum of 1 ml of whole blood will be collected at Visit 2 and a minimum of 3 mls of whole blood will be collected at Visit 3 and at the ***end of the first efficacy follow-up period*** ~~final study~~ visit, using tubes with serum separator.

Section 5.5.3

Study Group	**Blood sampling timepoint**			**Antigen**	**No. subjects**
	Timing	**Month**	**Visit no.**		
A, B, C & D	Post II	10	***End of 1st efficacy period visit***	all	800

Section 6.4

Subset Definitions

All subjects who have not completed the follow-up visit at 1 year of age as of October 31, 2002, will have an extended follow-up for rotavirus gastroenteritis for one more year with an additional follow-up visit at approximately 24 months of age. The number of subjects in this case is expected to be approximately 1000.

Section 8.1.2

Subjects enrolled in this study will be followed from the day of first vaccination until ***2*** years of age for the occurrence of gastroenteritis.

Synopsis (primary endpoint) and Section 10.1

- Occurrence of any rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period.

Synopsis (secondary endpoints) and Section 10.2

Efficacy endpoints

For the subset of subjects who receive two doses of HRV or placebo (N=2076).

- Occurrence of severe rotavirus gastroenteritis during-the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Occurrence of rotavirus gastroenteritis due to virus types heterologous to vaccine strain during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Occurrence of any and severe pure rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Occurrence of rotavirus gastroenteritis in which there is at least one other pathogen during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.
- Occurrence of hospitalization for rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.

For the subset of subjects who receive three doses of HRV or placebo (N~200):

- Occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the ***first*** efficacy follow-up period.

For the subset of subjects who participate in a second year of efficacy follow-up (until age 24 months):

- ***For the subset of subjects who receive two doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.***
- ***For the subset of subjects who receive two doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the second efficacy follow-up period.***
- ***For the subset of subjects who receive three doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.***
- ***For the subset of subjects who receive three doses of HRV or placebo, occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the second efficacy follow-up period***.

Immunogenicity endpoints

For the subset of subjects who receive two doses of HRV or placebo (N=2076).

- Serum rotavirus IgA antibody titers at Visit 1 and the ***end of the first efficacy follow-up period*** ~~final~~ visit and at Visits 2 and 3 in a subset (N=800).

Section 10.3
ATP cohort for efficacy

The ATP cohort for efficacy will be used to evaluate efficacy and the persistence of immune response at the ***end of the first efficacy follow-up period*** ~~final~~ ~~study~~ visit.

Section 10.4
The primary objective is to demonstrate that, for a range of viral concentration ($10^{4.7}$-ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of SB Biologicals' HRV vaccine, two doses of SB Biologicals' HRV vaccine given concomitantly with routine vaccinations can

prevent rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period following vaccination.

With respect to the year 2 efficacy follow-up, considering an attack rate of 12% for any gastroenteritis, a 60% VE and a sample size of 200 in each vaccine group, the power to detect a statistically significant vaccine effect with the pooled vaccine group and each vaccine group is 88% and 67% (2 sided fisher exact test, alpha=5%, no adjustment for multiplicity

Section 10.5

The final analysis will be performed at the end of the ***first*** efficacy follow-up period, after all enrolled subjects have completed the study visit ***at the end of the first efficacy follow-up period.*** Two interim analyses will be performed on immunogenicity and reactogenicity of the vaccines to provide early information on dose selection. ***An interim analysis on efficacy against any and severe rotavirus gastroenteritis will be performed to obtain early efficacy data.*** The interim results will be ***descriptive*** limited to summaries by group.

Analysis of data collected during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be presented in an annex.

Section 10.5.3

In addition, for all antigens, the distribution of antibody titers two months after the second dose and at ***the end of the first efficacy follow-up period*** ~~final~~ study visit will be displayed using reverse cumulative curves.

Section 10.5.4

Efficacy in the first efficacy follow-up period

The vaccine efficacy rate (VE) for subjects who received 2 doses of HRV vaccine or placebo, expressed as 100% X (1-Relative Risk), will be calculated for pooled vaccine groups and for each vaccine group, with their 95% CI (see Appendix J for mathematical detail) against:

- any and severe rotavirus gastroenteritis during-the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period,

- rotavirus gastroenteritis due to virus types heterologous to vaccine strain ***occurring two weeks after dose 2 until the end of the first efficacy follow-up period***. (amended: 12-FEB-2001)

- any and severe pure rotavirus gastroenteritis occurring two weeks after dose 2 until the end of the ***first*** efficacy follow-up period,

- mixed rotavirus gastroenteritis occurring during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period,

- any hospitalization for rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period,

The primary objective is to demonstrate that pooled HRV vaccine groups can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period, and subsequently that the HRV vaccine with a viral concentration of $10^{5.8}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period, and subsequently that the HRV vaccine with a viral concentration of $10^{5.2}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period, and subsequently that the HRV vaccine with a viral concentration of $10^{4.7}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period.

The efficacy of the pooled vaccine groups will be first evaluated. If the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period following vaccination in the pooled HRV groups is statistically significantly lower than in the placebo group (two-sided Fisher Exact test: $p < 0.05$), one will conclude that the efficacy of the pooled HRV vaccine groups in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period has been demonstrated.

If in addition the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-

up period following vaccination in the HRV group with a viral concentration of $10^{5.8}$ ffu is statistically significantly lower than in the placebo group (two-sided Fisher Exact test : $p < 0.05$), one will conclude that the efficacy of the HRV vaccine with a viral concentration of $10^{5.8}$ ffu in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period has also been demonstrated.

And, if in addition the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period following vaccination in the HRV group with a viral concentration of $10^{5.2}$ ffu is statistically significantly lower than in the placebo group (two-sided Fisher Exact test : $p < 0.05$), one will conclude that the efficacy of the HRV vaccine with a viral concentration of $10^{5.2}$ ffu in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period has also been demonstrated.

And, if in addition the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the ***first*** efficacy follow-up period following vaccination in the HRV group with a viral concentration of $10^{4.7}$ ffu is statistically significantly lower than the placebo group (two-sided Fisher Exact test: $p < 0.05$), one will conclude that the efficacy of the HRV vaccine with a viral concentration of $10^{4.7}$ ffu in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the ***first*** efficacy follow-up period has also been demonstrated.

For the subset of subjects who receive 3 doses of HRV or placebo:
the proportion of subjects reporting any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the ***first*** efficacy follow-up period will be calculated by group and for pooled vaccine groups.

Efficacy in the second efficacy follow-up period

The vaccine efficacy rate

- ***from the end of the first efficacy period up to the end of the second efficacy period***

- ***from two weeks post last HRV/placebo dose up to the end of the second efficacy period***

will be calculated for the pooled vaccine groups and for each vaccine group, with their 95% CI.

More specifically, this will be done for

- ***any (severe and hospitalized, respectively) rotavirus gastroenteritis,***
- ***any (severe and hospitalized, respectively) rotavirus gastroenteritis due to G1 types***
- ***any (severe and hospitalized, respectively) rotavirus gastroenteritis due to virus types heterologous to vaccine strain***

provided the number of cases is sufficient.

The above analyses will be performed separately for the subgroup of subjects enrolled in the 2-vaccine-dose cohort and the subgroup of subjects enrolled in the 3-vaccine-dose cohort.

Appendix N

Appendix N was added to the protocol for supplemental subject information and informed consent for study participants who will be followed until the end of the second efficacy follow-up period.

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Date of amendment 3	May 3, 2002
Date of amendment 4	July 11, 2002
Date of amendment 5	**September 20, 2002**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002

Approved by: Clinical Development Manager	[redacted]	23/09/02 dd-mm-yy
Head Biometrician	[redacted]	23/09/02 dd-mm-yy
Investigators	Dr. [redacted]	dd-mm-yy
	Dr. [redacted]	dd-mm-yy
	Dr. [redacted]	dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/006 (Rota-006)
Date of approval	Final – October 20, 2000
Date of amendment 1	February 12, 2001
Date of modification	May 14, 2001
Date of site-specific amendment	October 10, 2001
Date of amendment 2	December 11, 2001
Date of amendment 3	May 3, 2002
Date of amendment 4	July 11, 2002
Date of amendment 5	**September 20, 2002**
Title	A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.}$ and $10^{5.5}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine. (amended: 12-FEB-2001)

Approved by:
Clinical Development Manager

[redacted] dd-mm-yy

Head Biometrician

[redacted] dd-mm-yy

Investigators

[redacted] 4 November 2002
dd-mm-yy

Dr [redacted] dd-mm-yy

Dra [redacted] dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002

Approved by:
Clinical Development Manager

[redacted] dd-mm-yy

Head Biometrician

[redacted] dd-mm-yy

Investigators

Dr [redacted] dd-mm-yy

24/09/02

Dr [redacted] dd-mm-yy

Dra [redacted] dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002

Approved by:		
Director	[redacted]	dd-mm-yy
Head Biometrician	[redacted]	dd-mm-yy
Investigators	Dr. [redacted]	dd-mm-yy
	Dr [redacted]	dd-mm-yy
	[redacted] Dra [redacted]	14 OCT 2002 dd-mm-yy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium
Protocol Amendment Approval
Rota-006
444563/006

Protocol Title: A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Amendment 6
Date 26 March 2003

Coordinating Author: [redacted] Scientific Writer

Rationale/background for changes: This amendment was done

- to implement the use of a 'Standard Verbal Autopsy Questionnaire' as per the IDMC's recommendation,
- to remove co-pathogen testing for all subjects during the second year of efficacy follow-up,
- to reflect the termination of follow-up of Mexican subjects after the end of the 2003 rotavirus season in Mexico and
- to reflect the interim analysis planned on efficacy assessment in the second year in Mexico.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003

The following items in bold italics were amended on 26 March 2003:

Synopsis:

Rationale

Efficacy during a second year ***of efficacy follow-up period*** will be evaluated in a subset of children (about 1000).

Study Design

For the subset of subjects who participate in a second year of efficacy follow-up (until age ***18*** **-** 24 months), the intended duration of the study, per subject, will be approximately ***16*** **-** 22 months.

Study Procedure

A subset of subjects (N ~ 200) enrolled in Brazil ~~and Venezuela~~ will receive a third dose of the HRV vaccine or placebo along with blood sampling at Visit 3

Study visit at the end of the second ***year of*** efficacy follow-up ~~period (2 Years of Age~~ ***approximately 18 – 24 months of age***).

For the subset of subjects who participate in a second year of efficacy follow-up (until age 18 – 24 months)

Analyses

~~An~~ **Two** interim analysis on efficacy against any and severe rotavirus gastroenteritis will be performed to obtain early efficacy data.

Definitions

Second year of efficacy follow-up period: approximately 1000 subject will be followed for a second efficacy analysis either until the age of two years (for subjects from Brazil and Venezuela) or until the end of the 2003 rotavirus season (for subjects from Mexico)

Table of contents

ANNEX 1 (provided as a separate pdf document): The Standard Verbal Autopsy Questionnaire

Glossary of terms:

First year of **efficacy follow-up period:** Each subject will be followed for the efficacy analysis starting from two weeks post dose 2 until the age of

approximately one year ~~(approximately two years for a subset of about 1000 subjects)~~.
Second year of efficacy follow-up period: Approximately 1000 subject will be followed for a second efficacy analysis either until the age of two years (for subjects from Brazil and Venezuela) or until the end of the 2003 rotavirus season (for subjects from Mexico).

Rationale:
Efficacy during a second year ***of efficacy follow-up period*** will be evaluated in a subset of children (about 1000).

Section 3:
A subset of subjects (N ~ 200) enrolled in Brazil ~~and Venezuela~~ will receive a third dose of the HRV vaccine or placebo along with blood sampling at Visit 3

For the subset of subjects who participate in a second year of efficacy follow-up (until age ***18 -*** 24 months), the intended duration of the study, per subject, will be approximately ***16 -*** 22 months.

For these subjects the first ***year of*** efficacy follow-up study visit will take place at approximately one year of age: a blood sample will not be taken from this subset at this visit. (amended: 3-MAY-2002) (amended: 20-SEP-2002)
Study visit at the end of the second ***year of*** efficacy follow-up ~~period~~ (~~2 Years of Age~~ ***approximately 18 – 24 months of age***)

Section 5.3:

Table : ~~**Post vacc 2 MO 22,**~~ ***18 – 24 Mo***

Size of Interval **Brazil & Venezuela:335–395 days**
Mexico: June 1 -> 30, 2003 (after the end of rotavirus season)

Section 5.4:
~~**2 Year of Age**~~ **18 – 24 months of age (Brazil and Venezuela: 335–395 days after first efficacy follow-up visit) (Mexico : June 1 -> 30, 2003 after the end of RV season)**

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003

Section 5.5.2

During the first year of life, if rotavirus is detected (by rapid rotavirus detection kit) in the stool sample, part of the stool sample should be analysed locally for culture of enteric pathogens such as Salmonella, Shigella, and Campylobacter. ***During the second year of efficacy follow-up, the stool samples will be tested only for rotavirus, there will be no local testing for the presence of enteric pathogens.***

Section 5.5.3:

Study Group	Blood sampling timepoint			Antigen	No. subjects
	Timing	Month	Visit no.		
A, B, C & D	Post II MO 10	10	End of 1st efficacy period visit	~~all~~ ***concomitant*** rotavirus ~~only~~	800 ~~1276~~ ***2155***#

Section 6.4:

All subjects who have not completed the follow-up visit at 1 year of age as of October 31, 2002, will have an extended follow-up for rotavirus gastroenteritis for one more year with an additional follow-up visit at approximately ***18*** **-** 24 months of age.

In all, the subset that provides additional blood samples will contain ***approximately 800*** subjects and the subset that provides stool samples on day 0 and day 7 will contain ***approximately*** 400 subjects. (amended: 12-FEB-2001).

A subset of approximately 200 subjects among the last enrolled in Brazil ~~and Venezuela~~ will constitute the subset that will receive three doses of study vaccine/placebo. (amended: 3-MAY-2002). ***The sub-group that receives 3 doses is constituted of about 121 subjects (and not 200 as mentioned above) as the protocol was not approved in Venezuela. As outlined in the study procedures, these subjects also provide stool samples.***

Section 8.1.2

Subjects enrolled in this study will be followed from the day of first vaccination until ~~***2*** years of age~~ study end for the occurrence of gastroenteritis.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003

Section 8.5.2:
The Standard Verbal Autopsy Questionnaire (see Annex 1) (19) should be completed and transmitted by the investigator (or designee), in addition to the SAE report, for all deaths during the study period irrespective of relationship to vaccination and whether a written autopsy is performed or not. The Standard Verbal Autopsy Questionnaire does not replace the written autopsy. Refer to Annex 1.

[redacted]

Section 10.2:
For the subset of subjects who participate in a second year of efficacy follow-up (until age 18 - 24 months)

First year of *efficacy follow-up period*: Each subject will be followed for the efficacy analysis starting from two weeks post dose 2 until the age of approximately one year ~~(approximately two years for a subset of about 1000 subjects)~~.

Second year of efficacy follow-up period: approximately 1000 subject will be followed for a second efficacy analysis either until the age of two years (for subjects from Brazil and Venezuela) or until the end of the 2003 rotavirus season (for subjects from Mexico)

Section 10.5:
~~An~~ **Two** interim ~~analysis~~ **analyses** on efficacy against any and severe rotavirus gastroenteritis will be performed to obtain early efficacy data.

Section 10.6
An interim analysis on efficacy against any and severe rotavirus gastroenteritis at the end of the second efficacy follow-up period in Mexico will be performed to obtain early efficacy data. No study report will be written and distribution of the results will be strictly controlled. Unblinding at the level of individual data will be restricted to the statistician and the database administrator. No adjustment on the alpha or the power will be applied for the final analyses of efficacy. Considering an attack rate of 12% for any rotavirus gastroenteritis over the two efficacy follow-up periods, a 60% VE and a sample size of 60 subjects in each group, the power to detect a statistically significant vaccine effect with the pooled

vaccine group is 40% (2 sided fisher exact test, alpha=5%)

References:

World Health Organization. A Standard Verbal Autopsy Method for Investigating Causes of Death in Infants and Children. Geneva: World Health Organizatoin, 1999:1-78. (WHO/CDS/CSR/ISR/99.4).

Appendix C:

For the subjects who participate only in the first year of efficacy follow-up (until age 12 months), the intended study duration, ***per subject,*** will be approximately 10 months. ***For the subset of subjects who participate in a second year of efficacy follow-up (until age 18 - 24 months), the intended duration of the study, per subject, will be approximately 16 - 22 months.***

Appendix F:

Additional testing for other pathogens is done on rotavirus positive GE stool samples ***during the first year of efficacy follow-up, but not during the second year of efficacy follow-up***, as described in section 5.5.2.

Informed consent/ Subject information sheet (Appendix N):

ONLY FOR STUDY PARTICIPANTS WHO WILL BE FOLLOWED FOR EFFICACY FOR A SECOND YEAR ***UNTIL 18-24 MONTHS*** OF AGE

As your child has not yet completed the follow-up visit at approximately one year of age, we propose to follow him/her for a second year (until age ***18-24*** months). About 1000 children are expected to participate in the second year follow-up.

Interval between visit at 1 year old and visit at approximately ~~**2 years old**~~ ***18 – 24 months*** old.

You will continue the efficacy follow-up during the interval between follow-up visit at one year of age and follow-up visit at ***18-24 months*** ~~two years~~ of age.

Follow-up visit at approximately ~~**2 years**~~ ***18 – 24*** **of age** ***(Brazil and Venezuela: 2 years of age) (Mexico: June 1-> 30, 2003 after the end of RV season)***

We will test the stool samples for rotavirus ~~and some other pathogens~~.

document) (Amended: 26 March 2003)

Approved by: CDM/D title	[redacted]	31.03.2003 dd-mm-yyyy
Associate Director, Biometrics	[redacted]	31/3/2003 dd-mm-yyyy
Principal Investigator	[redacted]	dd-mm-yyyy
Principal Investigator	[redacted]	08/05/2003 dd-mm-yyyy
Principal Investigator	Dra [redacted] M.D.	dd-mm-yyyy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003

Approved by: CDM/D title	[redacted]	dd-mm-yyyy
Associate Director, Biometrics	[redacted]	dd-mm-yyyy
Principal Investigator	[redacted]	September 12, 2003 dd-mm-yyyy
Principal Investigator	Dr [redacted]	dd-mm-yyyy
Principal Investigator	Dra [redacted] M.D.	dd-mm-yyyy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003

Document) (Modified: 26 March 2003)

Approved by
CDM/D title

[redacted] dd-mm-yyyy

Associate Director, Biometrics

[redacted] dd-mm-yyyy

Principal Investigator

Dr. [redacted] dd-mm-yyyy

Principal Investigator

Dr [redacted] dd-mm-yyyy

Principal Investigator

[redacted]

(Dr [redacted] M.D. 30 APR 2003 dd-mm-yyyy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium
Protocol Amendment Approval
Rota-006
444563/006

Protocol Title: A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

Amendment 7
Date 21 August 2003

Coordinating Author: [redacted] Scientific Writer

Rationale/background for changes: This amendment was done to allow study end in October 2003 by terminating the second year follow-up of subjects in Brazil and Venezuela.

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

The following items in strikethrough or bold italics were amended on 21 August 2003:

Synopsis (Rationale) and Section 1.1:
Efficacy during a second ~~year of~~ efficacy follow-up period will be evaluated in a subset of children (about 1000).

Synopsis (Secondary Objectives) and Section 2.2:
*Second ~~year~~ follow-up **period** (for a subset of about 1000 subjects)*

- To evaluate the efficacy of the HRV vaccine during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period, and during the period starting from 2 weeks after the last HRV/placebo dose until the end of the second efficacy follow-up period.

  The endpoints evaluated for this second ***follow-up period*** analysis (severity and nature of disease, study groups and subsets) will be similar to those evaluated during the first year of follow-up (refer to section 10.5.4 for details).

Synopsis (Study Design) and Section 3:
- All subjects will be followed for efficacy until one year of age and a subset, about 1000 subjects, will be followed for efficacy until ***a maximum of*** two years of age.
- For the subset of subjects who participate in ~~a~~ ***the*** second ~~year of~~ efficacy follow-up ***period*** (until ***maximum*** age ~~18~~ – 24 months), the intended duration of the study, per subject, will be ~~approximately 16~~ –22 months ***at most***.

Synopsis (Study Participation) and Section 3:
Study visit at the end of the second ~~year of~~ efficacy follow-up ***period*** (~~approximately 18~~ – 24 months of age **maximum**) – Efficacy Follow-up. This will be the final study visit for the subjects who participate in a second ~~year of~~ efficacy follow-up ***period***.

Synopsis (Secondary Endpoints) and Section 10.2:
For the subset of subjects who participate in a second ~~year of~~ efficacy follow-up

period (until ***maximum*** age ~~18~~ 24 months):

Definitions and Section 10.2:
Second ~~year of~~ efficacy follow-up ***period:*** Approximately 1000 subject will be followed for a second efficacy analysis either until ~~the age of two years~~ ***October 2003*** (for subjects from Brazil and Venezuela) or until the end of the 2003 rotavirus season (for subjects from Mexico).

Section 5.2:
For the subjects who participate in ~~a~~ ***the*** second ~~year of~~ efficacy follow-up ***period***, the follow-up visit at the end of the second efficacy follow-up period (at ***maximum*** 24 months of age) will be the final visit.

Section 5.3:
§For subjects who participate in a second ~~year of~~ efficacy follow-up ***period***

Size of interval (First efficacy follow-up visit → Second efficacy follow-up visit)
Brazil and Venezuela: ~~335–395 days~~ ***until 01 -> 31 October 2003***

Section 5.4:
Second efficacy follow-up visit: Efficacy Follow-up
Maximum ~~18~~ 24 months of age (Brazil and Venezuela: ~~335–395 days~~ ***until 01 -> 31 October 2003***)

These subjects will be followed until 2 years of age **maximum** (all of them), thus the final visit will be at end of second efficacy follow-up (**maximum** 24 months of age).

- Study Conclusion for the subjects who participate in the second ~~year of~~ efficacy follow-up ***period.***

Section 5.5.2:
Also, stool samples will be collected during each episode of gastroenteritis which occur from the first dose until **study end** ~~2 years of age~~. During the second ~~year of~~ efficacy follow-up ***period***, the stool samples will be tested only for rotavirus, there will be no local testing for the presence of enteric pathogens.

Section 6.4:
All subjects who have not completed the follow-up visit at 1 year of age as of October 31, 2002, will have an extended follow-up for rotavirus gastroenteritis ~~for one more year~~ with an additional follow-up visit at approximately 18 - 24 months of age.

Appendix C:

- For the subjects who participate only in the first year of efficacy follow-up (until age 12 months), the intended duration of the study, per subject, will be approximately 10 months for subjects. For the subset of subjects who participate in a second ~~year of~~ efficacy follow-up ***period*** (until ***maximum*** age ~~18~~– 24 months), the intended duration of the study, per subject, will be ~~approximately 16~~– 22 months ***at most***.

Appendix F:
Additional testing for other pathogens is done on rotavirus positive GE stool samples during the first year of efficacy follow-up, but not during the second ~~year of~~ efficacy follow-up ***period***, as described in section 5.5.2.

Appendix N:
Follow-up visit at ~~approximately~~ maximum ~~18~~– 24 of age (Brazil and Venezuela: ~~2 years of age~~ *until 01 -> 31 October 2003*) (Mexico: June 1-> 30, 2003 after the end of RV season)

Approved by: Clinical Development Manager	[redacted]	21.08.2003 dd-mm-yyyy
Associate Director, Biometrics	[redacted]	21/8/2003 dd-mm-yyyy
Principal Investigator	Dr. [redacted]	dd-mm-yyyy
Principal Investigator	Dr. [redacted]	dd-mm-yyyy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Approved by:		
Clinical Development Manager	[redacted]	dd-mm-yyyy
Associate Director, Biometrics	[redacted]	dd-mm-yyyy
Principal Investigator	[redacted] Dr [redacted]	12 September 2003 dd-mm-yyyy
Principal Investigator	Dr. [redacted]	dd-mm-yyyy
Principal Investigator	Dra [redacted] M.D.	dd-mm-yyyy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Section 6.4:

All subjects who have not completed the follow-up visit at 1 year of age as of October 31, 2002, will have an extended follow-up for rotavirus gastroenteritis ~~for one more year~~ with an additional follow-up visit at approximately 18 - 24 months of age.

Appendix C:

- For the subjects who participate only in the first year of efficacy follow-up (until age 12 months), the intended duration of the study, per subject, will be approximately 18 months for subjects. For the subset of subjects who participate in a second ~~year of~~ efficacy follow-up *period* (until *maximum* age ~~18~~ - 24 months), the intended duration of the study, per subject, will be ~~approximately 16~~ - 22 months *at most*.

Appendix F:

Additional testing for other pathogens is done on rotavirus positive GE stool samples during the first year of efficacy follow-up, but not during the second ~~year~~ of efficacy follow-up *period*, as described in section 5.5.2.

Appendix N:

Follow-up visit at ~~approximately~~ maximum ~~18~~ - 24 of age (Brazil and Venezuela: ~~2 years of age~~ *until 01 -> 31 October 2003*) (Mexico: June 1-> 30, 2003 after the end of RV season)

Approved by:

Clinical Development Manager [redacted] dd-mm-yyyy

Associate Director, Biometrics [redacted] dd-mm-yyyy

Principal Investigator [redacted] dd-mm-yyyy

Principal Investigator [redacted] 24/09/2003 dd-mm-yyyy

Amendment 1: February 12, 200
Modification: May 14, 200
Site-specific amendment: October 10, 200
Amendment 2: December 11, 200
Amendment 3: May 3, 200
Amendment 4: July 11, 200
Amendment 5: September 20, 200
Amendment 6: 26 March 200
Amendment 7: 21 August 200

Principal Investigator	Dra [redacted] M.D.	dd-mm-yyyy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

We will test the stool samples for rotavirus ~~and some other pathogens~~.

Annex 1: Standard Verbal Autopsy Questionnaire (Provided as a separate pdf document) (amended: 26 March 2003)

Approved by: CDM/D title	[redacted]	dd-mm-yyyy
Associate Director, Biometrics	[redacted]	dd-mm-yyyy
Principal Investigator	Dr [redacted]	dd-mm-yyyy
Principal Investigator	Dr. [redacted]	dd-mm-yyyy
Principal Investigator	[redacted]	03/SEP/2003 dd-mm-yyyy

Amendment 1: February 12, 2001
Modification: May 14, 2001
Site-specific amendment: October 10, 2001
Amendment 2: December 11, 2001
Amendment 3: May 3, 2002
Amendment 4: July 11, 2002
Amendment 5: September 20, 2002
Amendment 6: 26 March 2003
Amendment 7: 21 August 2003

Protocol
(incl. SIS-IC)

SmithKline Beecham Mexico,
Av. Insurgentes Sur 1605 piso 20,
Colonia San Jose Insurgentes; Mexico D.F., CP04800

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/008 (Rota-008) – Annex to protocol 444563/006 (Rota-006)
Date of approval	Final – November 29, 2000
Annex Title	To assess the impact of breast milk lactadherin, breast milk rotavirus IgA antibodies and maternal IgG antibodies on the immunogenicity of SB Biologicals' rotavirus vaccine.
Medical Monitor (Mexico)	[redacted] M.D. SmithKline Beecham Mexico, Av. Insurgentes Sur 1605 piso 20, Colonia San Jose Insurgentes Mexico D.F. CP04800 Tel: [redacted] Fax: [redacted]
Clinical Study Director	[redacted] M.D. Av. Comandante Guaranys, 447 Jacarepagua, Rio de Janeiro Brasil 22775-610 Tel: [redacted] Fax: [redacted]
(Principal) Investigator	Dr. [redacted] [redacted] Mexico

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the clinical study as described and will adhere to the Ethical and Regulatory Considerations stated. I have read and understood the contents of the Investigator Brochure.

Signature Date

(Principal) Investigator name

Synopsis

Annex Title

To assess the impact of breast milk lactadherin, breast milk rotavirus IgA antibodies and maternal IgG antibodies on the immunogenicity of SB Biologicals' rotavirus vaccine.

Indication

Not applicable.

Study Population

Mothers of children enrolled in study protocol **444563/006 dated October 20, 2000**. The child has to be part of the subset selected for blood samples.

Rationale

It has been reported that breast milk lactadherin might protect against symptomatic rotavirus infection.

The study protocol **444563/006 dated October 20, 2000** to be conducted in Mexico will enroll children to assess the immunogenicity of SB Biologicals' rotavirus vaccine. In the view that SB Biological's rotavirus vaccine is of human origin, it is plausible that the lactadherin protein might influence the immunogenicity of the rotavirus vaccine.

The **main objective** of this protocol is to determine the breast milk lactadherin concentration in the breast milk of the mothers and to assess its influence on the immunogenicity of the rotavirus vaccine.

In addition , the protocol will determine

- the IgA rotavirus antibody level in the breast milk and assess its influence on the immunogencity of the rotavirus vaccine.
- the maternal IgG rotavirus antibody level in the serum of the children enrolled in study protocol **444563/006 dated October 20, 2000** and assess its influence on the immunogenicity of the rotavirus vaccine
- the IgG rotavirus antibody level in the serum of the mothers.

Objectives

Primary

- To explore the influence of breast milk lactadherin on the vaccine take in children enrolled in study **444563/006 dated October 20, 2000**.

*Vaccine take is defined as the appearance of serum IgA to rotavirus in post-immunization sera at a titer ≥ 20 U/ml or vaccine virus shedding in any stool sample collected from Visit 1 to Visit 3 in

children enrolled in study **444563/006 dated October 20, 2000**.

Secondary

- To explore the influence of breast milk lactadherin on serum* rotavirus IgA antibody titers in children enrolled in study 444563/006 dated October 20, 2000.
- To explore the influence of pre-existing maternal breast milk IgA antibodies on vaccine take and on serum* rotavirus IgA antibody titers in children enrolled in study **444563/006 dated October 20, 2000**.
- To explore the influence of pre-existing maternal IgG antibodies in the serum* of the children on vaccine take and on serum* rotavirus IgA antibody titers in children enrolled in study **444563/006 dated October 20, 2000**.
- To assess the serum IgG antibody titers in serum samples collected from the mothers at Visit 1 and Visit 4.

* serum of the children enrolled in protocol **444653/006 dated October 20, 2000**.

Study design

- Experimental design: Open study. The study subjects are mothers whose children are enrolled in SB Biological's protocol **444563/006 dated October 20, 2000**. The child has to be part of the subset selected for blood samples.
- Study will be conducted Mexico.

THE INTENDED DURATION OF THE STUDY, PER MOTHER, WILL BE APPROXIMATELY 2 MONTHS.

- Four study visits:

Visit 1 (day 0) – informed consent, breast milk sample and blood sample to measure anti-rotavirus IgG antibodies.

Visit 2 (day 7 ± 1): breast milk sample

Visit 3 (month 2): breast milk sample

Visit 4 (day 7 ± 1 after Visit 3): breast milk sample, blood sample to measure anti-rotavirus IgG antibodies and study conclusion.

- Data collection will be by paper case report forms (CRF).
- Recruitment time will be discussed in the recruitment plan, which is summarised in Appendix C.

Number of subjects	Approximately 200 mothers will be enrolled.
Primary endpoints	• Concentration of breast milk lactadherin at each visit. • Vaccine take at visit 2 and 3 in the children enrolled in study **444563/006 dated October 20, 2000**.
Secondary endpoints	• Serum IgA antibody titers at visit 1, 2 and 3 in the children enrolled in **444563/006 dated October 20, 2000**. • Serum IgG antibody titers at visit 1, 2 and 3 in the children enrolled in **444563/006 dated October 20, 2000**. • IgA antibody titers in the breast milk at each visit. • IgG antibody titers in serum samples collected from the mothers at Visit 1 and visit 4.

Table of Contents

Page No.

1 INTRODUCTION 9

2 OBJECTIVES 10

2.1 PRIMARY OBJECTIVE 10
2.2 SECONDARY OBJECTIVES 10

3 STUDY DESIGN OVERVIEW 10

4 STUDY COHORT 11

4.1 NUMBER OF SUBJECTS / CENTERS 11
4.2 INCLUSION CRITERIA 11
4.3 EXCLUSION CRITERIA 12
4.4 ELIMINATION CRITERIA 12
4.5 CONTRAINDICATIONS TO VACCINATION 12

5 CONDUCT OF STUDY 12

5.1 ETHICS AND REGULATORY CONSIDERATIONS 12
5.1.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC) 12
5.1.2 Informed consent 13
5.2 GENERAL STUDY ASPECTS 15
5.3 OUTLINE OF STUDY PROCEDURES 16
5.4 DETAILED DESCRIPTION OF STUDY STAGES/VISITS 16
5.5 SAMPLE HANDLING AND ANALYSIS 17
5.5.1 Treatment and storage of biological samples 17
5.5.2 Laboratory assays 17

6 STUDY VACCINE(S) AND ADMINISTRATION 18

6.1 STUDY VACCINE 18
6.2 DOSAGE AND ADMINISTRATION 18
6.3 STORAGE 18
6.4 TREATMENT ALLOCATION AND RANDOMISATION 19
6.5 METHOD OF BLINDING AND BREAKING THE STUDY BLIND 19
6.6 REPLACEMENT OF UNUSABLE VACCINE DOSES 19
6.7 PACKAGING 19
6.8 VACCINE ACCOUNTABILITY 19
6.9 CONCOMITANT MEDICATION/TREATMENT 19

7 HEALTH ECONOMICS 19

8 ADVERSE EVENTS 19

9 SUBJECT COMPLETION AND DROP-OUT 20

9.1 DEFINITION 20
9.2 PROCEDURES FOR HANDLING DROP-OUTS 20
9.3 REASONS FOR DROP-OUT..... 20

10 DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES 20

10.1 PRIMARY ENDPOINTS 20
10.2 SECONDARY ENDPOINTS..... 20
10.3 STUDY COHORTS/DATA SETS TO BE EVALUATED..... 21
10.4 ESTIMATED SAMPLE SIZE..... 21
10.5 FINAL ANALYSES 21
10.5.1 Analysis of demographics..... 21
10.5.2 Analysis of safety 21
10.5.3 Analysis of immunogenicity..... 21
10.6 INTERIM ANALYSIS..... 21

11 ADMINISTRATIVE MATTERS 22

12 REFERENCES 22

APPENDIX

Appendix A: World Medical Association Declaration of Helsinki
Appendix B: Administrative Matters
Appendix C: Overview of the recruitment plan
Appendix D: Handling of Biological Samples Collected by the Investigator
Instructions for Handling of Serum Samples
Appendix E: Sample Subject Information and Informed Consent

List of Abbreviations

ANOVA	—	Analysis of variance
CI	—	Confidence interval
CRF	—	Case report form
ELISA	—	Enzyme-linked immunosorbent assay
GMT	—	Geometric mean antibody titer
IEC	—	Independent Ethics Committee
Ig	—	Immune globulin
IRB	—	Institutional Review Board
ml	—	Milliliter
PID	—	Patient identification number
SAS	—	Statistical Analysis System
SB	—	SmithKline Beecham

Glossary of Terms

Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in analysis (see Section 10.3 for details on criteria for evaluability).
Medical Monitor:	An individual medically qualified to assure the responsibilities of the sponsor especially as regards the ethics, clinical safety of a study and the assessment of adverse events.
Clinical Study Monitor:	An individual assigned by SmithKline Beecham who is responsible for assuring proper conduct of a clinical study at one or more investigational sites.
Subject(s):	Term used throughout the protocol to denote the enrolled individual(s).
Vaccine take:	For subjects previously uninfected with rotavirus before vaccination, appearance of serum IgA to rotavirus in post-immunization sera at a titer ≥ 20 U/ml or vaccine virus shedding in any stool sample collected from Visit 1 to Visit 3 in study 444563/006.

1 Introduction

It has been reported that breast milk lactadherin, a 46 kDa glycoprotein, present in breast milk mucin can prevent rotaviral disease by binding to rotavirus thereby blocking viral binding to host-cell receptors. Breast milk lactadherin is thus representative of a class of non-antibody glycoconjugates in human milk that function as competitive homologue to host-cell receptor and that have specific inhibitory activity against specific pathogens (1).

The clinical relevance of the role of breast milk lactadherin in rotavirus infection was assessed in Mexico city by following 200 infants from birth up to 2 years of age. Breast milk samples were collected from the mothers while blood and stool samples were collected from the infants at regular intervals. Of these 200 children, 31 developed rotavirus infection (15 with symptomatic infection and 16 with asymptomatic infection). The median breast milk lactadherin concentration in breast milk samples collected before rotavirus infection was 48.4 (range 5.6-180) mcg/ml in children with asymptomatic infection, and 29.2 (range 6.2-103.2) mcg/ml in children with symptomatic infection. This study showed that breast milk lactadherin concentration might be associated with protection of breastfed infants from symptomatic rotavirus infection (2).

SB Biologicals has developed a live, attenuated human-derived rotavirus vaccine (RIX4414). It is plausible that since the active ingredient in SB Biologicals' rotavirus vaccine candidate is a human rotavirus strain, there is a potential that breast milk lactadherin could influence the immunogencity of the rotavirus vaccine in breast-fed infants.

The **main objective** of this protocol is to determine the breast milk lactadherin concentration in the breast milk of the mothers and to assess its influence on the immunogenicity of the rotavirus vaccine.

In addition , the protocol will determine

- the IgA rotavirus antibody level in the breast milk and assess its influence on the immunogencity of the rotavirus vaccine.
- the maternal IgG rotavirus antibody level in the serum of the children enrolled in study protocol **444563/006 dated October 20, 2000** and assess its influence on the immunogenicity of the rotavirus vaccine
- the IgG rotavirus antibody level in the serum of the mothers.

The protocol describes the procedures to be followed for the mothers for the assessment of breast milk lactadherin. These procedures will be in addition to the procedures described in study protocol **444563/006 dated October 20, 2000**.

2 Objectives

2.1 Primary objective

- To explore the influence of breast milk lactadherin on the vaccine take in children enrolled in study **444563/006 dated October 20, 2000**.

*Vaccine take is defined as the appearance of serum IgA to rotavirus in post-immunization sera at a titer ≥ 20 U/ml or vaccine virus shedding in any stool sample collected from Visit 1 to Visit 3 in children enrolled in study **444563/006 dated October 20, 2000**

2.2 Secondary objectives

- To explore the influence of breast milk lactadherin on serum* rotavirus IgA antibody titers in children enrolled in study 444563/006 dated October 20, 2000.
- To explore the influence of pre-existing maternal breast milk IgA antibodies on vaccine take and on serum* rotavirus IgA antibody titers in children enrolled in study **444563/006 dated October 20, 2000**.
- To explore the influence of pre-existing maternal IgG antibodies in the serum* of the children on vaccine take and on serum* rotavirus IgA antibody titers in children enrolled in study **444563/006 dated October 20, 2000**.
- To assess the serum IgG antibody titers in serum samples collected from the mothers at Visit 1 and Visit 4.

* serum of the children enrolled in protocol **444653/006 dated October 20, 2000**

3 Study Design Overview

- Experimental design: Open study. The study subjects are mothers whose children are enrolled in SB Biological's protocol **444563/006 dated October 20, 2000**. The child has to be part of the subset selected for blood samples.
- Study will be conducted Mexico.

- The intended duration of the study, per mother, will be approximately 2 months.
- Four study visits:

Visit 1 (day 0) – informed consent, breast milk sample and blood sample to measure anti-rotavirus IgG antibodies.

Visit 2 (day 7 ± 1): breast milk sample

Visit 3 (month 2): breast milk sample

Visit 4 (day 7 ± 1 after Visit 3): breast milk sample, blood sample to measure anti-rotavirus IgG antibodies and study conclusion.

- Data collection will be by paper case report forms (CRF).
- Recruitment time will be discussed in the recruitment plan, which is summarised in Appendix C.

4 Study Cohort

4.1 Number of subjects / centers

This study will be conducted in Mexico.

The **protocol 444563/006 dated October 20, 2000** will enroll 2640 children. Three countries participate in the enrollment of all 2640 study subjects. Mexico will enroll a total of 800 subjects out of these 2640 subjects. About 200 of these Mexican subjects will constitute the subset that will provide blood sample**. The mothers of these 200 children will be asked to participate in this protocol**

Only subjects for whom the investigator believes the requirements of the protocol will be complied with should be enrolled in the study.

See Section 10.4 for a description of the criteria used in the justification of the sample size.

See Appendix C for details of the recruitment plan.

4.2 Inclusion criteria

- Mother of a child enrolled in study **444563/006 dated October 20, 2000**. The child has to be part of the subset selected for blood samples.
- Mother should be breastfeeding at the time of the first visit

4.3 Exclusion criteria

Not applicable.

4.4 Elimination criteria

Not applicable.

4.5 Contraindications to vaccination

Not applicable. Enrolled mothers will not receive any vaccine.

5 Conduct of Study

5.1 Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice, the Declaration of Helsinki (Protocol Appendix A), and local rules and regulations of the country.

5.1.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The IRB/IEC must be constituted according to the local laws/customs of each participating country. It is recommended that it should include:

- At least five members.
- At least one member whose primary area of interest is in a non-scientific area.
- At least one member who is independent of the institution/ study site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the study should vote/ provide opinion on a study-related matter.

A list of IRB/IEC members and their qualifications should be obtained by the investigator.

This protocol and any other documents that the IRB/IEC may need to fulfil its responsibilities, including subject recruitment procedures, and information about payments and compensation available to subjects, will be submitted to an appropriate Committee or Board by the investigator or designate, and their written unconditional approval should be in the possession of the investigator and the sponsor before commencement of the study. Relevant SmithKline Beecham Biologicals data will be supplied by the SmithKline Beecham study monitor via the investigator (or designate) to the hospital/ university/ independent IRB/IEC for the protocol's review and approval. Verification of IRB/IEC unconditional

approval of the protocol and the written informed consent statement will be transmitted by the investigator (or designate) using the standard notification form, generally prior to shipment of vaccine supplies and CRFs to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and state the date of review.

No deviations from, or changes to, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor(s), telephone number(s)). Modifications are submitted to the IRB/IEC for information only. However, written verification that the modification was submitted should be obtained. Approvals/ verifications must be transmitted in writing to SmithKline Beecham Study Monitor.

The IRB/IEC must be informed by the investigator (or designate) of

- all subsequent protocol amendments/modifications, informed consent changes or revisions of other documents originally submitted for review
- serious and/or unexpected adverse events occurring during the study, where required
- all subsequent protocol modifications (for information)
- new information that may affect adversely the safety of the subjects or the conduct of the study
- an annual update and/or request for re-approval, where required
- when the study has been completed, where required.

5.1.2 Informed consent

The principles of informed consent in the current edition of the Declaration of Helsinki (Protocol Appendix A) should be implemented in each clinical study before any protocol-specified procedures or interventions are carried out. Informed consent will be obtained in accordance with 21 CFR 50.25.

Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC.

The written consent document will embody the elements of informed consent as described in the current edition of the Declaration of Helsinki, will adhere to the ICH Harmonized Tripartite Guideline for Good Clinical Practice and will also comply with local regulations.

An investigator or designate will describe the protocol to potential subjects face to face. The Subject Information and Consent Form may be read to the subjects, but, in any event, the investigator shall give the subjects ample opportunity to inquire about details of the study and ask any questions before dating and signing the Consent Form. All illiterate individuals will have the study, the Subject Information and Consent Form explained to them point by point by the interviewer in the presence of an impartial witness. The witness should personally sign and personally date the consent form.

Subjects must be informed that the trial involves research, purpose of the trial, those aspects of the trial that are experimental, expected benefits, possible risks (including a statement that the particular treatment or procedure may involve risks to the subject which are currently unforeseeable), the expected duration of the subject's participation in the trial, the subject's responsibilities, the approximate number of subjects involved in the trial, procedures of the research study including all invasive procedures and the probability for random assignment to treatment groups. Subjects be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. They must also be informed of alternative procedures that may be available and the important potential benefits and risks of these available alternative procedures. Subjects must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. Subjects must be informed of the anticipated financial expenses, if any, to the subject for participating in the trial as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They must be informed whom to contact (e.g. the investigator) for answers to any questions relating to the research project. Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. Subjects must be informed that the subject's participation is voluntary and that they are free to withdraw from the study for any reason at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in the trial. The extent of the confidentiality of subject records must be defined, and subjects must be informed that applicable data protection legislation will be complied with. Subjects must be informed that the monitor(s), auditor(s), IRB/IEC, and the regulatory authority (ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and

regulations and that, by signing a written informed consent form, the subject is authorizing such access. Subjects must be informed that records identifying the subject will be kept confidential, and to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the subject's identity will remain confidential.

The consent form generated by the investigator with the assistance of SmithKline Beecham Biologicals, must be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC and be acceptable to SmithKline Beecham Biologicals. Consent forms must be in a language fully comprehensible to the prospective subject. Informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subject, and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or SmithKline Beecham professional and Regulatory Compliance persons. The subject should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to the subjects. Oral witnessed consent will replace written consent only in countries where the local custom is contrary or if the subject's incapacity precludes this and provided that the local legal obligations are fulfilled.

5.2 General study aspects

The **main objective** of this protocol is to determine the breast milk lactadherin concentration in the breast milk of the mothers and to assess its influence on the immunogenicity of the rotavirus vaccine. The protocol will be implemented in mothers of subjects (children) enrolled in Mexico in study **444653/006 dated October 20, 2000**.

Breast milk samples will be collected from approximately 200 mothers on each day that their child receives a dose of human rotavirus study vaccine and on day 7 ± 1 after each study vaccine dose by emptying the entire contents of one breast using a breast pump into a sterile container. The milk samples will be transported on ice, and within 4 hours of collection frozen and stored at -70°C. Two blood sample will be collected to determine the rotavirus IgG

There is no additional study procedure to be implemented on the children participating in the study 444563/006.

5.3 Outline of study procedures

Visit	**VISIT 1**	**VISIT 2***	**VISIT 3**	**VISIT 4***
Sampling timepoint	**Pre vacc 1 Day 0**	**Post vacc 1 Day 7±1**	**Post vacc 1 Day 60**	**Post vacc 2 Day 7±1**
Check of inclusion criteria	•			
Informed consent	•			
Breast milk sample	•	•	•	•
Blood sample from mother	•			•
Study conclusion				•

*these visits can be home visits by field workers; vacc refers to the child's rotavirus vaccination

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed. These intervals determine a subject's evaluability in the according to protocol analyses (see Sections 4.4 and 10.3 for details of criteria for evaluability and cohorts to be analyzed).

Intervals between study visits*

Interval	Size of interval
1 (Visit 1→Visit 2)	6-8 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→Visit 4)	6-8 days

*The date of the previous visit is the reference date.

5.4 Detailed description of study stages/visits

Visit 1: Visit 1 of enrolled child (Vaccine Dose 1 given to the child)

- Written informed consent signed by the subject.
- Check of inclusion criteria.
- Collection of blood sample to measure anti-rotavirus IgG antibodies: a minimum of 1 ml of whole blood to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.
- Collection of 15 to 20 ml of breast milk sample according to instructions in section 5.5.1.

Visit 2: Day 7 ± 1 after visit 1

- Collection of 15 to 20 ml of breast milk sample according to instructions in section 5.5.1

Visit 3: Visit 2 of enrolled child (Vaccine Dose 2 given to the child)

- Collection of 15 to 20 ml of breast milk sample according to instructions in section 5.5.1.

Visit 4: Day 7 ± 1 after visit 3

- Collection of blood sample to measure anti-rotavirus IgG antibodies: a minimum of 1 ml of whole blood to provide a minimum of 0.4 ml of serum according to instructions in Appendix D.
- Collection of 15 to 20 ml of breast milk sample according to instructions in section 5.5.1.
- Study conclusion.

5.5 Sample handling and analysis

5.5.1 Treatment and storage of biological samples

See Appendix D of the protocol for details of handling and storage of biological samples.

Breast milk samples
The membrane is separated from the milk fat globule, the sample is centrifuged and the non-lipid portion dialysed and lyophilised. Just before analysis the samples are reconstituted in phosphate-buffered saline. Protein content will be determined by the method of Lowry et al.

Blood samples
After centrifugation and serum separation, samples will be stored at -20°C until collection by the sponsor.

5.5.2 Laboratory assays

Breast milk samples
Breast milk lactadherin will be measured in appropriate dilutions of milk by endpoint dilution RIBA.

Anti-rotavirus IgA antibodies in breast milk will be measured by ELISA. The current cut-off is 20 U/ml, based on the technical assay by Ward [3, 4] and adapted by SB Biologicals.

Serum sample collected from the mothers
Serum IgG antibodies will be measured by ELISA method (assay developed and performed by Dr Ward). Microplates are coated with cell lysate .Specific binding is detected in wells coated with lysate obtained from cells infected with rotavirus (positive wells); non specific binding is measured in wells coated with lysate obtained from non infected cells (negative wells). Each sample/standard is incubated in the two types of wells. After incubation of the samples and washing step, biotinylated anti-human IgG is added. Wells are washed and avidin-HRP is added. After a washing step, OPD is used as chromogen/colorimetric reaction. Optical densities are recorded at 492 nm. For each sample/standard, specific optical densities are calculated by making the difference between positive and negative wells. Using a four -parameter logistic equation, a standard curve is drawn and samples concentrations, expressed in ELISA units/ml , are interpreted on the standard curve.

Serum sample collected from the children
As described in the main **protocol 444563/006 dated October 20, 2000,** some children will provide blood samples. The blood samples will be used to perform the tests described in the main protocol 444563/006 dated October 20, 2000.
No additional blood sample is required from the children under the procedures of this protocol. However, one additional test will performed on the blood samples collected under the study **protocol 444563/006 dated October 20, 2000** :

Serum IgG antibodies by ELISA (assay developed and performed by Dr Ward)

6 Study Vaccine(s) and Administration

6.1 Study vaccine

Not applicable. Enrolled mothers will not receive any vaccine.

6.2 Dosage and administration

Not applicable.

6.3 Storage

Not applicable.

6.4 Treatment allocation and randomisation

When a mother is eligible and has given informed consent, the study personnel will allocate a subject identification number. The mother's subject number will be the same as the patient identification number (PID) allocated to her child.

The subject number will also be used as identification number for all data collected on the subject under the study.

6.5 Method of blinding and breaking the study blind

In order to preserve the blining of study 444563/006, the analysis of the study will be performed at the stuyd end of 444563/006.

6.6 Replacement of unusable vaccine doses

Not applicable.

6.7 Packaging

Not applicable.

6.8 Vaccine accountability

Not applicable.

6.9 Concomitant medication/treatment

Not applicable.

7 Health Economics

Not applicable.

8 Adverse Events

Not applicable. Enrolled mothers will not receive any vaccine.

9 Subject Completion and Drop-out

9.1 Definition

From an analysis perspective, any subject who does not come back for Visit 4 is considered as a drop-out. A subject who returns for Visit 4 is considered to have completed the study.

9.2 Procedures for handling drop-outs

Investigators should make an attempt to contact those subjects who do not return for scheduled visits or follow-up. Information gathered should be described on the Study Conclusion page of the CRF and on Medication/Adverse event forms.

9.3 Reasons for drop-out

It should be specified on the Study Conclusion page of the CRF, which of the following possible reasons were responsible for drop-out of the subject from the study:

- Protocol violation (specify)
- Consent withdrawal, not due to an adverse event
- Migrated/moved from the study area
- Lost to follow-up
- Other (specify).

10 Data Evaluation: criteria for evaluation of objectives

10.1 Primary endpoints

- Concentration of breast milk lactadherin at each visit.
- Vaccine take at visit 2 and 3 in the children enrolled in study **444563/006 dated October 20, 2000**.

10.2 Secondary endpoints

- Serum IgA antibody titers at visit 1, 2 and 3 in the children enrolled in **444563/006 dated October 20, 2000**.
- Serum IgG antibody titers at visit 1, 2 and 3 in the children enrolled in **444563/006 dated October 20, 2000**.
- IgA antibody titers in the breast milk at each visit.

- IgG antibody titers in serum samples collected from the mothers at Visit 1 and Visit 4.

10.3 Study cohorts/data sets to be evaluated

Total cohort

The Total cohort will include all enrolled subjects for whom data are available.

10.4 Estimated sample size

Due to the exploratory feature of the study, the sample size is based on feasability only. It is anticipated that about 200 mother will be enrolled in this study (50 in each study group of 444563/006).

10.5 Final analyses

The data from the study 444563/006 will be used in the anlaysis of the immunogencity. Please refer to protocol 444653/006 dated October 20, 2000 for the definition of the groups

10.5.1 Analysis of demographics

The mean, range and standard deviation of age in years will be calculated per group. The racial composition will be presented.

10.5.2 Analysis of safety

Not applicable. Enrolled mothers will not receive any vaccine.

10.5.3 Analysis of immunogenicity

The impact of lactadherin and maternal antibodies (maternal anti-IgA in breast milk, anti-IgG in serum of the children)

- **ON THE VACCINE TAKE WILL BE EXPLORED USING A LOGISTICAL REGRESSION**
- On anti-IgA antibodies in serum of the children will be explored using an ANOVA model

The results of these analyses should be interpreted cautiously because of the exploratory feature.

10.6 Interim analysis

Not applicable.

11 Administrative Matters

To comply with Good Clinical Practice important administrative obligations relating to investigator responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled. See Appendix B for details.

12 References

1. Yolken RH, Peterson JA et al. Human milk mucin inhibits rotavirus replication and prevents experimental gastroenteritis. J Clin Invest 1992;90:1984-91.

2. Role of human-milk breast milk lactadherin in protection against symptomatic rotavirus infection. Newburg DS, Peterson JA et al. Lancet 1998;351:1160-4.

3. Bernstein DI, Smith VE, Sherwood JR et al. Safety and immunogenicity of a live attenuated human rotavirus 89-12 vaccine. Vaccine 1998;16:381-7.

4. Bernstein DI, Sack DA, Rothstein E, Reisinger K et al. Efficacy of live attenuated human rotavirus vaccine 89-12 in infants: a randomised placebo-controlled trial. Lancet 1999;354:287-90.

Appendix A: World Medical Association Declaration of Helsinki

Recommendations guiding physicians
in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly
Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
41st World Medical Assembly
Hong Kong, September 1989
and the
48th General Assembly
Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic

for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of research, even though the subject has given his or her consent.

Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical research)

In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

The refusal of the patient to participate in a study must never interfere with the physician–patient relationship.

If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

The Physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the

life and health of that person on whom biomedical research is being carried out.

The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

Appendix B: Administrative Matters

I. Responsibilities of the Investigator

To ensure that he/she has sufficient time to conduct and complete the study and has adequate staff and appropriate facilities which are available for the duration of the study and to ensure that other studies do not divert essential subjects or facilities away from the study at hand.

To submit an up-to-date curriculum vitae and other credentials (e.g. medical license number in the United States) to the sponsor and—where required—to relevant authorities.

To acquire the normal ranges for laboratory tests performed locally and, if required by local regulations, obtain the Laboratory License or Certification.

To retain no clinical samples (including serum samples) on site without the approval of SmithKline Beecham Biologicals and the express written informed consent of the subject and/or the subject's legally authorized representative.

To perform no other biological assays at the investigator site except those described in the protocol or its amendment(s).

To prepare and maintain adequate case histories designed to record observations and other data pertinent to the study.

To conduct the study in compliance with the protocol and appendices.

To cooperate with a representative of SmithKline Beecham Biologicals in the monitoring process of the study and in resolution of queries about the data.

II. Protocol Amendments and modifications

No changes to the study protocol will be allowed unless discussed in detail with the SmithKline Beecham Biologicals' Clinical Project Manager and filed as an amendment/modification to this protocol.

Any amendment/modification to the protocol will be adhered to by the participating center(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments is required prior to implementation; modifications are submitted to IRBs/IECs for information only.

III. Sponsor's Termination of Study

SmithKline Beecham Biologicals reserves the right to discontinue the clinical study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be tendered.

IV. Case Report Form Instructions

Prior to screening the first potential participant, the investigator will provide a list showing the signature and hand-written initials of all individuals authorized to make or change entries on CRFs. If the authorized individuals should change during the study, the investigator is to inform SmithKline Beecham Biologicals.

Case report forms (and subject diary cards, if applicable), will be supplied by SmithKline Beecham Biologicals for recording all data. It is the responsibility of the investigator or co-investigator to ensure that CRFs (and subject diary cards) are legible and completely filled in with a black ink fountain or ballpoint pen.

Errors must be corrected by drawing a single line through the incorrect entry and writing in the new value/data positioned as close to the original as possible. The correction must then be initialed, dated and justified, where necessary, by the authorized individual making the change. The original entry must not be obliterated, overwritten or erased when a correction is made.

When a subject completes a visit, it is anticipated that relevant sections of the CRF will be completed by the investigator (or designated staff) within 24 hours of the last data becoming available, but in no case later than 5 days. Similarly, when a subject completes a study, it is anticipated that all relevant CRF pages will be completed within 24 hours of the last data becoming available, but in no case later than 5 days. This also applies to forms for potential study participants who were screened but not randomized to a study group.

As soon as the subject has completed/withdrawn from the study and the CRF is completed the principal investigator or designated physician(s) under his/her supervision will sign the study conclusion pages of the CRF to confirm that they have reviewed the data and that the data are completed and accurate.

An original (top copy) CRF or log sheets must be submitted for all subjects who have undergone protocol specific procedures, whether or not the subject completed the study.

While completed CRFs will be reviewed by a SmithKline Beecham Biologicals' professional monitor at the study site, errors detected by subsequent in-house CRF review may necessitate clarification or correction of errors and documentation and approval by the investigator. Wherever possible the investigator should assist in clarification or correction of errors detected after study finalization within 48 hours of their being brought to the attention of the investigator.

Any questions or comments related to the CRF should be directed to the assigned Site Monitor.

V. Monitoring by SmithKline Beecham (i.e. the Sponsor)

Monitoring visits by a professional representative of the sponsor will be scheduled to take place before entry of the first subject, during the study at appropriate intervals and after the last subject has completed. It is anticipated that monitoring visits will occur at a minimum frequency of once every eight weeks.

These visits are for the purpose of confirming that SmithKline Beecham Biologicals sponsored studies are being conducted in compliance with the relevant Good Clinical Practice regulations/ guidelines, verifying adherence to the protocol and the completeness and exactness of data entered on the CRF/RDE screens and Vaccine Inventory Forms. The monitor will verify CRF/RDE entries by comparing them with the source data/documents that will be made available by the investigator for this purpose. Data to be recorded directly into the CRF/RDE screens will be specified in the source documentation agreement form that is contained in both the monitor's and investigator's study file. In cases of RDE, the monitor will mark completed and approved screens at each visit. At the end of the monitoring visit, the monitor will transmit the electronic data.

The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits.

VI. Archiving of Data

The investigator/ institution should maintain all study documentation until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of the clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The investigator/ institution should take measures to prevent accidental or premature destruction of these documents. In studies which employ Remote Data Entry, these data will be will be in the CD Rom format.

Similarly, the sponsor-specific study documentation should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or if needed by the sponsor. The sponsor should inform the investigator/institution in writing of the need for record retention and should notify the investigator/institution in writing when the study-related records are no longer needed.

VII. Audits

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for SmithKline Beecham Biologicals or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an investigator signs the protocol, he agrees to permit Drug Regulatory Agency and SmithKline Beecham Biologicals' audits, providing direct access to source data/ documents. Furthermore, if an

investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application.

SmithKline Beecham Biologicals has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of vaccine development. SmithKline Beecham Biologicals has a Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that SmithKline Beecham Biologicals sponsored studies are in accordance with the Good Clinical Practices and that relevant regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take 1 to 2 days. The SmithKline Beecham Biologicals audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on vaccine accountability. The SmithKline Beecham Biologicals audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring SmithKline Beecham Biologicals of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- IRB/IEC approval
- Vaccine accountability
- Approved study protocol and amendments
- Informed consent of the subjects (written or witnessed oral consent)
- Medical records supportive of CRF data
- Reports to the IRB/IEC and the sponsor
- Record retention.

SmithKline Beecham Biologicals will gladly help investigators prepare for an inspection.

VIII. Confidentiality and Publication

You agree that all information communicated to you by SmithKline Beecham Biologicals is the exclusive property of SmithKline Beecham Biologicals and you will ensure that the same shall be kept strictly

confidential by you or any other person connected with the work and shall not be disclosed, either orally or in written form, by you or such person to any third party without the prior written consent of SmithKline Beecham Biologicals. You shall communicate the results of the work promptly to SmithKline Beecham Biologicals.

We agree that you shall have the right to publish or permit the publication of any information or material relating to or arising out of the work after prior submission to us provided that if we shall so request you will delay publication for a maximum of six months to enable us to protect our rights in such information or material. Any proposed publication or presentation (e.g. manuscript, abstract or poster) for submission to a journal or scientific meeting, should be sent to the Site Monitor prior to submission, together with confirmation that any other author(s) has seen and agreed the proposed publication/presentation. SmithKline Beecham Biologicals will undertake to comment on such documents within four weeks.

All rights and interests worldwide in any inventions, know-how or other intellectual or industrial property rights which arise during the course of and/or as a result of the clinical study which is the subject of this Protocol or which otherwise arise from the information or materials supplied under this Agreement, shall be assigned to, vest in and remain the property of SmithKline Beecham plc.

Appendix C: Overview of the recruitment plan

- Study 444563/008 will be a site-specific protocol implemented in Mexico as an annex to study protocol **444563/006 dated October 20, 2000**.
- Target enrollment will be 200 subjects. Eligible subjects will be mothers of children enrolled in study protocol **444563/006 dated October 20, 2000** and are part of the subset selected for blood samples.
- Enrollment will start around January 15, 2001.
- All subjects will be enrolled within a period of 4 months.
- Study duration will be approximately 2 months per subject
- The recruitment will be monitored by the site monitor.

Appendix D: Handling of Biological Samples Collected by the Investigator

Instructions for Handling of Serum Samples

When materials are provided by SmithKline Beecham Biologicals, it is mandatory that all clinical samples (including serum samples) be collected using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement.

Instructions for Handling of Serum Samples

1. Collection

The whole blood (by capillary or venous route) should be collected observing appropriate aseptic conditions. It is recommended that Vacutainer® tubes WITH integrated serum separator (e.g. Becton-Dickinson Vacutainer® SST or Corvac® Sherwood Medical) be used so as to minimize the risk of hemolysis and to avoid blood cell contamination of the serum when transferring to standard serum tubes.

2. Serum separation

These guidelines aim to ensure high quality serum by minimizing the risk of hemolysis, blood cell contamination of the serum or serum adverse cell toxicity at testing.

- For separation of serum using Vacutainer® tubes, the instructions provided by the manufacturer should be followed. Siliconized tubes should never be used (cell toxicity). Often the manufacturer's instruction states that the relative centrifugal acceleration known also as "G" must be "between 1000 and 1300 G" with tubes spinning for 10 minutes. Error in calculation of centrifuge speed can occur when laboratory personnel confuse "G" acceleration with "RPM" (revolutions per minute). The speed of centrifugation must be calculated using the "G" rate provided in the manufacturer's instructions and the radius of the centrifuge head. After measuring the radius of the centrifuge machine, a speed/acceleration nomograph must be employed to determine the centrifuge speed in "RPM".

- Following separation, the serum should be aseptically transferred to the appropriate standard tube using a sterile disposable pipette. The serum should be transferred as gently as possible to avoid blood cell contamination. Only one aliquot should be prepared.

- The tube should not be overfilled (max. 3/4 of the total volume) to allow room for expansion upon freezing.

- The tube should be identified by the appropriate, provided label (see point 3).

3. Labelling

The standard labels provided by SmithKline Beecham Biologicals should be used to label each serum sample.

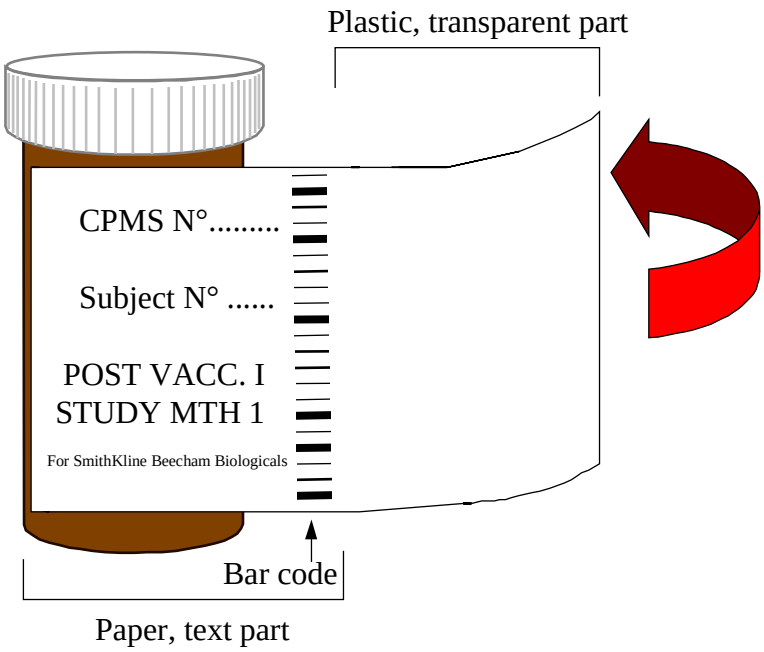
If necessary, any hand-written additions to the labels should be made using indelible ink.

The label should be attached to the tube as follows (see diagram):

- first attach the paper part of the label to the tube

- then wrap the label around the tube so that the transparent, plastic part of the label overlaps with the label text and bar code and shields them.

This will ensure optimal label attachment.



Labels should not be attached to caps.

4. Sorting and storage

Tubes should be placed in the SmithKline Beecham Biologicals carton or cardboard box in numerical order from left to right, starting from the lower left hand corner, beginning with the pre vaccination samples series, then with the post vaccination sample series.

The tubes of serum should be stored in a vertical position at a temperature between -20°C and -70°C until shipment to core laboratories A and/or B. Wherever possible, a backup facility for storage of serum samples should be available.

Instructions for Handling of breast milk samples

Breast milk samples will be collected on the day of each dose and on day 7 after each dose from the mothers by emptying the entire contents of one breast using a breast pump into a sterile container. The milk samples will be transported on ice, and within 4 hours of collection frozen and stored at -70°C.

Appendix E: Sample Subject Information and Informed Consent

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/008 (Rota-008) – Annex to protocol 444563/006 (Rota-006)
Date of approval	Final – November 28, 2000
Annex Title	To assess the impact of breast milk lactadherin, breast milk rotavirus IgA antibodies and maternal IgG antibodies on the immunogenicity of SB Biologicals' rotavirus vaccine.
Medical Monitor (Mexico)	[redacted] M.D. SmithKline Beecham Mexico, Av. Insurgentes Sur 1605 piso 20, Colonia San Jose Insurgentes Mexico D.F. CP04800 Tel: [redacted] Fax: [redacted]
Clinical Study Director	[redacted] M.D. Av. Comandante Guaranys, 447 Jacarepagua, Rio de Janeiro Brasil 22775-610 Tel: [redacted] Fax: [redacted]
(Principal) Investigator	Dr. [redacted] [redacted] [redacted] [redacted] [redacted] Mexico

Introduction

In order to decide whether your child should be in this research study, you should know about the study's risks and benefits. Then you can make an informed decision. This consent form gives you detailed information about the study. A member of the research team will discuss all of this information with you. He or she will explain the study's purpose, procedures to be performed, any risks and discomforts of the study, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you want your child to be in the study. If you do, you will be asked to sign this form.

This consent form may contain words that you do not understand. Please ask the study doctor or staff to explain anything unfamiliar.

You will receive a signed copy of this consent form for your records.

SmithKline Beecham Biologicals has developed a new investigational rotavirus vaccine based on a human rotavirus. The human rotavirus in the new vaccine has been weakened so that when a child swallows it, it causes only a mild infection with few to no symptoms. The child is expected to become immune from the weakened human rotavirus infection. It has been recently reported by some researchers that certain components normally present in breast milk can prevent disease caused by rotavirus. It is therefore possible that the composition of your breast milk can affect how your child's immune system (part of body that fights infection) reacts to the investigational vaccine.

This site specific protocol will therefore analyze the composition of your breast milk with respective to the components that are reported to prevent rotavirus infection, and assess if breast milk composition has any effect on your child’s response to the vaccine. The protocol will also analyze the composition of your blood.

Approval

This study protocol has been reviewed and accepted by an independent ethics review committee/Institutional review board.

Study Participation

Mothers of approximately 200 eligible subjects (50 subjects per study group) enrolled in Mexico in study 444563/006 will be asked to participate in this annex study protocol. If your child was one of the 200 infants enrolled, you will be given this informed consent document along with the informed consent document for your child’s participation. If you sign the consent form, you and your child will participate in this study.

Your participation will involve providing breast milk samples on each day your child receives a study vaccine dose and on day 7 after each study vaccine dose. In addition, you will provide 2 blood samples. The study procedures at each visit are outlined below.

Visit 1:

- You will sign the written informed consent.
- Inclusion criteria will be checked by the study personnel.
- Collection of 1 ml of blood sample
- Collection of 15 to 20 ml of breast milk sample.

Visit 2:

- Collection of 15 to 20 ml of breast milk sample.

Visit 3:

- Collection of 15 to 20 ml of breast milk sample.

Visit 4:

- Collection of 1 ml of blood sample
- Collection of 15 to 20 ml of breast milk sample.
- Study conclusion

Risks associated with the study

No potential risks are foreseen from the collection of breast milk samples and blood sample from you.

Voluntary participation

Your participation is voluntary. Refusal to take part or continue with the study will involve no penalty or loss of benefits or attention to which you are otherwise entitled to receive from your healthcare provider. You are entitled to receive a signed copy of this form.

Alternative measures of prevention

Not applicable.

Confidentiality and source document review

You understand and consent to the following:

It will be necessary for representatives of SmithKline Beecham or possibly health authorities to access your medical records. Your participation in the study will be treated as confidential, that is,

any personally identifiable information will be held and processed under secure conditions at SmithKline Beecham (or an agent of SmithKline Beecham) with access limited to appropriate SmithKline Beecham staff or other authorized agents having a requirement to maintain the confidentiality of the information. You will not be referred to by name in any report of the study. Your identity will not be disclosed to any person, except for the purposes described above and in the event of a medical emergency or if required by law.

Your data will be processed electronically to determine the outcome of this study, and to provide it to health authorities. Your data may be transferred to other countries (such as USA, Europe) for these purposes SmithKline Beecham complies with internal procedures to protect personal information even in countries whose data privacy laws are less strict than those of this country. The data may also be used for other medical research purposes.

You may be entitled under law to access your / your child's/ward's personal data and to have any justifiable corrections made. If you wish to do so, you should request this from the doctor conducting the study.

Right to ask questions and/or withdraw from the study

You may ask questions about the study. Although your continuous support is appreciated, you have the right to withdraw from the study at any time and you/he/she will be under no further obligation for blood samplings or vaccinations.

If you have any questions, please contact:

Name of investigator: _____

Address of investigator: _____

_____

Telephone number of investigator: _____

Fax number of investigator: _____

Benefits of the study:

By participating in this scientific study you will help the sponsors in studying the effect of breast milk on the investigational vaccine. Your participation will thus help in development of the rotavirus vaccine that will benefit other children may benefit from it in the future.

Compensation:

If you become ill or injured as a result of taking part in this clinical study, medical treatment will be provided according to good clinical practice and costs of such treatment will be paid for by SmithKline Beecham Biologicals. All participants in the study are covered by global insurance policy contracted by SmithKline Beecham Biologicals. If you have any questions concerning the availability of medical care or if you think you have experienced a research-related illness or injury, please contact:

Name of investigator: _____

Address of investigator: _____

_____

Telephone number of investigator: _____

Fax number of investigator: _____

Informed Consent

The aims and procedures of the clinical study has been clearly explained to me and I have read the preceding information sheet and understood the information provided. I agree to be enrolled in the study. I understand that I have the right to decline to enter the study and to withdraw from it at any time for any reasons, without consequence to my present or future health care and attention which I receive from my healthcare provider. I have been made aware of my right to access and request correction of my personal data. I acknowledge that I have received a copy of this form for future reference.

I, _____ ,
(subject's first name and family name)

hereby freely give my consent to take part in this [clinical/vaccine] study.

Participant's signature: _____

Participant's main address: _____

Participant's phone number: _____

Date: _____ **Time:** _____
(DD-MM-YY)

Witness: _____

Statement by Doctor, Nurse or Project Assistant who conducted the informed consent discussion:

I have carefully explained the nature, demands and foreseeable risks and benefits of the vaccination study to the person named above and witnessed the completion of the written consent form.

Name: _____

Signature: _____

Designation: _____

Date: _____ **Time:** _____
(DD-MM-YY)

Protocol Investigator Agreement

SmithKline Beecham Mexico,
Av. Insurgentes Sur 1605 piso 20,
Colonia San Jose Insurgentes; Mexico D.F., CP04800

Study vaccine(s)	SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine
CPMS Protocol No.	444563/008 (Rota-008) – Annex to protocol 444563/006 (Rota-006)
Date of approval	Final – November 29, 2000
Annex Title	To assess the impact of breast milk lactadherin, breast milk rotavirus IgA antibodies and maternal IgG antibodies on the immunogenicity of SB Biologicals' rotavirus vaccine.
Medical Monitor (Mexico)	[redacted] M.D. SmithKline Beecham Mexico, Av. Insurgentes Sur 1605 piso 20, Colonia San Jose Insurgentes Mexico D.F. CP04800 Tel: [redacted] Fax: [redacted]
Clinical Study Director	[redacted] M.D. Av. Comandante Guaranys, 447 Jacarepagua, Rio de Janeiro Brasil 22775-610 Tel: [redacted] Fax: [redacted]
(Principal) Investigator	Dr. [redacted] Mexico

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the clinical study as described and will adhere to the Ethical and Regulatory Considerations stated. I have read and understood the contents of th[redacted]

Si[redacted] Dec 15, 2000
Date

(Principal) Investigator name

SmithKline Beecham México,
Av. Insurgentes Sur 1605 piso 20,
Colonia San José Insurgentes; México D.F., C.P. 04800

Vacuna(s) del estudio	Vacuna de rotavirus humano vivo atenuado (RVH) de SmithKline Beecham Biologicals
CPMS Protocolo No.	444563/008 (Rota-008) – Anexo a protocolo 444563/006 (Rota-006)
Fecha de aprobación	Final – 29 de noviembre de 2000
Título del Anexo	Valorar el impacto de lactadherina de leche materna, anticuerpos IgA de rotavirus en leche materna y anticuerpos IgG maternos en la inmunogenicidad de la vacuna de rotavirus de SB Biologicals.
Supervisor (Monitor) Médico (México)	Dra. [redacted] SmithKline Beecham México, Av. Insurgentes Sur 1605 piso 20, Colonia San José Insurgentes México D.F. C.P. 04800 Tel: [redacted] Fax: [redacted]
Director de Estudio Clínico	Dra. [redacted] Av. Comandante Guaranys, 447 Jacarepagua, Río de Janeiro Brasil 22775-610 Tel: [redacted] Fax: [redacted]
Investigador (Principal)	Dr. [redacted] México

Yo, el abajo firmante, he revisado este protocolo, incluyendo los Apéndices y llevaré a cabo el estudio clínico como se describe, apegándome a las Consideraciones Éticas y Normativas estipuladas. Así mismo he leído y en[redacted]to del Investigador.

Fir[redacted] 03/Dic/00
Fecha

Nombre del investigador (Principal)

GlaxoSmithKline

Sample CRF

Center	Subject identification	Subject Number
|__|__|__|	|__|__| First name |__|__| Family name	|__|__|__|__|__|

SmithKline Beecham

CONFIDENTIAL

WORKBOOK

444563/006 (Rota-006)

SmithKline Beecham Biologicals s.a.

Rue de l'institut 89, B – 1330 Rixensart, Belgium
Tel: [redacted] Fax: [redacted]

Version 11.2

GENERAL INSTRUCTIONS

Print clearly in **CAPITAL LETTERS** using a **black** fountain or ball-point pen and press firmly so that all copies are legible. Insert the writing board beneath all copies of the form being completed. Fill in the subject number on every page and answer all questions except where otherwise indicated.

Do not write in shaded areas which are qualified **"For SB"**. Information written in these areas **are not the responsibility of the investigator**.
For each subject's **INITIALS**, please enter the first two letters of the first name and the first two letters of the family name.

ABBREVIATIONS: Abbreviations for medical conditions, clinical events or drug names should not be used. Units and route of administration of medication may be abbreviated. NA: not applicable.

IMPORTANT: Errors should be crossed out with a single line and the alteration made as near to the original as possible.
All alterations must be printed, initialled and dated by the investigator or authorized staff.

DATE

Use the following three-letter abbreviations for each month:

January	=	JAN
February	=	FEB
March	=	MAR
April	=	APR
May	=	MAY
June	=	JUN
July	=	JUL
August	=	AUG
September	=	SEP
October	=	OCT
November	=	NOV
December	=	DEC

Example : | 0 1 | | J A N | | 2 0 0 0 | = 1st January 2000
day month year

TIME

Unless specified otherwise, use the 24 hour clock :
Example: | 1 5 | : | 3 0 | = 3.30 p.m.
hours min

The **Medication** section, the **Concomitant Vaccination** section, the **Non-Serious Adverse Events** section and the **Serious Adverse Event (SAE)** form must be checked for final assessment at the end of the study.

For all subjects enrolled, please complete the **Conclusion after the first rotavirus season and the Study conclusion** forms.

ADVERSE EVENT DEFINITIONS

INTENSITY FOR SOLICITED SYMPTOMS

Cough/runny nose

0 : Normal
1 : Cough/runny nose which is easily tolerated
2 : Cough/runny nose which interferes with daily activity
3 : Cough/runny nose which prevents daily activity

Irritability/Fussiness

0 : Behavior as usual
1 : Crying more than usual / no effect on normal activity
2 : Crying more than usual / interferes with normal activity
3 : Crying that cannot be comforted / prevents normal activity

Loss of appetite

0 : Normal
1 : Eating less than usual / no effect on normal activity
2 : Eating less than usual / interferes with normal activity
3 : Not eating at all

GASTROENTERITIS EPISODES

Any diarrhea defined as three or more looser than normal stools within a day.

INTENSITY FOR NON-SOLICITED SYMPTOMS

0 : No adverse event.
1 : An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 : An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3 : An adverse event which prevents normal, everyday activities
(In a young child, such an adverse event would, for example, prevent attendance at school/kindergarten/ a day-care center and would cause the parents/guardians to seek medical advice).

ADVERSE EVENT DEFINITIONS

CAUSALITY

In your opinion, did the vaccine(s) possibly contribute to the adverse event?

NO : The adverse event is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the adverse event.

YES: There is a reasonable possibility that the vaccine contributed to the adverse event.

OUTCOME

1 : Recovered
2 : Recovered with sequelae
3 : Ongoing at study conclusion active phase or safety follow-up (whichever is applicable)
4 : Died
5 : Unknown

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that:

1 : results in death
2 : is life threatening
3 : results in persistent or significant disability / incapacity
4 : requires in-patient hospitalization
5 : prolongation of existing hospitalization
6 : is a congenital anomaly / birth defect in the offspring of a study subject
7 : In addition, important medical events that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not results in hospitalization; or development of drug dependency or drug abuse).

For each serious adverse event, please fill in the **Serious Adverse Event (SAE)** form and contact SmithKline Beecham within 24 hours (one calendar day).

Although not considered as 'serious adverse events', cancers must be reported in the same way as serious adverse events.

SmithKline Beecham

FLOW SHEET

Age	2 months	4 months	6 months	1 year
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2**	**Post vacc 2 MO 6**
Informed consent	•			
Medical history	•			
Check of inclusion criteria	•			
Check of exclusion criteria	•			
Check of elimination criteria		•	•	•
Check of contraindications	•	•	•	
Randomisation	•			
Physical examination	•	•	•	•
Pre-vaccination body temperature	•	•	•	
Measure/record height and weight	•	•	•	•
Blood sampling	• (1 ml of blood)	• (1 ml of blood in a subset)	• (3 mls of blood in a subset)	• (3 mls of blood in a subset, 1 ml for all others)
Stool samples will be collected from a subset (N = 400) on the day of administration of dose 1 and dose 2 and on day 7 following each dose.	•	•		
Study Vaccine	•	•		
Routine Vaccination	•	•	•	
Daily post-vaccination recording of solicited symptoms (days 0–14) by parents/guardians	•	•		
Collection of stool samples	•	•	•	•
Recording of non serious adverse events within 42 days after dose 1 and dose 2, by investigator		•	•	
Contact (field visit) every week to check on the occurrence of any serious AE or gastroenteritis episodes	◊	◊	◊	◊
Return of diary cards	•	•	•	•
Diary card transcription		•	•	•
Documentation of routine EPI vaccines	•	•	•	•
Recording medication	•	•	•	
Reporting of Serious Adverse Events occurring throughout the study period	•	•	•	•
Study Conclusion				•

◊ is used to indicate a study procedure which does not require documentation in the individual eCRFs.

The double-line border following Visit 3 aims to distinguish the data that will be included in the analyses of immunogenicity/safety on all available data around June 30, 2001.

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed. These intervals determine a subject's evaluability in the according to protocol analyses.

Intervals between study visits*

Interval	Size of interval
1 (Visit 1→Visit 2)	49 - 83 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→Visit 4)	160 - 200 days

*The date of the previous visit is the reference date.

VISIT 1

6 to 12 weeks of age

DOSE 1

Informed Consent has to be obtained prior to any study procedure

ELIGIBILITY CHECKLIST

INCLUSION CRITERIA

All subjects enrolled must satisfy the following criteria at study entry :

1. A male or female child between, and including 6 and 12 weeks (42-90 days) of age at the time of the first vaccination.
2. Free of obvious health problems as established by medical history and clinical examination before entering into the study.
3. Written informed consent obtained from the parents or guardians of the subject.
4. Born after a gestation period (between 36 and 42 weeks) or a birth weight > 2000g.

EXCLUSION CRITERIA FOR ENROLMENT

The following criteria should be checked at the time of study entry. If any apply at the time of study entry, the subject must not be included in the study :

5. Use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the study vaccine or placebo or planned use during the study period.
6. Planned administration of a vaccine (including routine pediatric vaccines) not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.
7. Planned administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
8. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth. (Topical steroids are allowed.)
9. History of diphtheria, tetanus, pertussis, Hib disease and/ or hepatitis B.
10. Previous vaccination against diphtheria, tetanus, pertussis, and/or *Haemophilus influenzae* type b.
11. Use of antibiotics within 7 days preceding dose 1 (Warrants deferral of vaccination pending recovery of the subject).
12. Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the GI tract or other serious medical condition as determined by the investigator.
13. Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
14. History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.
15. Acute disease at time of enrollment. (Acute disease is defined as the presence of moderate or severe illness with fever i.e. temperature ≥ 37.5°C as measured by an axillary thermometer or ≥ 38.0°C as measured by a rectal thermometer). A temperature greater than or equal to these cut-off warrants deferral of the vaccination pending recovery of the subject.
16. Gastroenteritis within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).
17. Household contact with an immunosuppressed individual or pregnant women.
18. Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
19. Previous confirmed occurrence of rotavirus gastroenteritis.

ELIMINATION CRITERIA TO BE CHECKED AT VISITS 2 AND 3

The following criteria should be checked at Visits 2 and 3. If any become applicable during the study, the subject will not be required to discontinue the study but may be eliminated from the according-to-prtocol analysis.

- Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
- Use of antibiotics during the period starting from 7 days before dose 1 and 2 and ending 7 days after.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
- Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of vaccine(s) and ending 14 days after.
- Administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
- Administration of immunoglobulins and/or any blood products during the study period.
- Confirmed immunosuppressive or immunodeficient condition, including HIV.

ELIMINATION CRITERIA DURING THE STUDY FROM VISIT 3 TO VISIT 4

The following criteria should be checked at visit 4. If any become applicable during the study, the subject may be eliminated from the according-to-protocol analysis.

- Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
- Administration of immunoglobulins and/or any blood products during the study period.
- Confirmed immunosuppressive or immunodeficient condition, including HIV.

Contraindications and precautions for further doses

SB Biologicals' HRV vaccine or placebo:

The following adverse events constitute absolute contraindications to further administration of human rotavirus vaccine or placebo; if any of these adverse events occur during the study, the subject must not receive additional doses of vaccine or placebo but may continue other study procedures at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event :

- Hypersensitivity reaction due to the vaccine.
- Intussusception

The following adverse events constitute contraindications to administration of human rotavirus vaccine or placebo at a given point in time; if any one of these adverse events occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol or withdrawn at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event.

- Axillary/rectal temperature ≥37.5°C/38.0°C
- Gastroenteritis within 7 days preceding the study vaccine administration

DTPw-HB+Hib vaccine:

The following adverse events constitute absolute contraindications or precautions to further administration of DTPw-HB+Hib vaccine; if any of these adverse events occurs during the study, the subject must be withdrawn and must be followed until resolution of the event, as with any adverse event:

Absolute contraindications:

- Known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B or Hib vaccines.
- Encephalopathy (not due to another identifiable cause). This is defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, and/or generalized or focal seizures that persist more than a few hours, with failure to recover within 24 hours. Even though causation by DTP-containing vaccine cannot be established, no subsequent doses of pertussis vaccine should be given.

Precautions:

If the following adverse events occur in temporal relation to DTPw-HB+Hib vaccine administration, the decision to administer additional doses of DTPw-HB+Hib vaccine should be carefully considered:

- Fever ≥ 40.5°C/≥ 40.0°C (rectal/axillary temperature) within 48 hours of vaccination not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting >3 hours, occurring within 48 hours of vaccination.
- Seizures with or without fever occurring within 3 days of vaccination.

Protocol	Center	Visit	Date of visit	Subject Number
444563/006	|__|__|__|	**VISIT 1**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date : |__|__| |__|__|__| |__|__|__|__|
day month year

DEMOGRAPHICS

Subject initials : |__|__| |__|__|
First name Family name

Date of birth : |__|__| |__|__|__| |__|__|__|__|
day month year

Gender :
- ☐ Male
- ☐ Female

Race :
- ☐ (WH) White
- ☐ (BL) Black
- ☐ (OR) Oriental
- ☐ (OT) Other, please specify: _____

Height : |__|__|__| cm

Weight : |__|__|__| . |__| kg

Is the subject eligible for the study, according to the criteria listed hereby ?

- ☐ Yes
- ☐ No, please give the corresponding criterion number(s) : _____

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

GENERAL MEDICAL HISTORY / PHYSICAL EXAMINATION

Are you aware of any pre-existing conditions or signs and/or symptoms present in the subject prior to the start of the study ?

☐ No

☐ Yes, please check appropriate box(es) and give diagnosis

			PAST	CURRENT		DIAGNOSIS
____	10	Cutaneous	☐	☐	1	----------
			☐	☐	2	----------
____	5	Eyes	☐	☐	1	----------
			☐	☐	2	----------
____	6	Ears-nose-throat	☐	☐	1	----------
			☐	☐	2	----------
____	2	Cardiovascular	☐	☐	1	----------
			☐	☐	2	----------
____	3	Respiratory	☐	☐	1	----------
			☐	☐	2	----------
____	1	Gastrointestinal	☐	☐	1	----------
			☐	☐	2	----------
____	7	Musculoskeletal	☐	☐	1	----------
			☐	☐	2	----------
____	8	Neurological	☐	☐	1	----------
			☐	☐	2	----------
____	12	Genitourinary	☐	☐	1	----------
			☐	☐	2	----------
____	11	Haematology	☐	☐	1	----------
			☐	☐	2	----------
____	4	Allergies	☐	☐	1	----------
			☐	☐	2	----------
____	9	Endocrine	☐	☐	1	----------
			☐	☐	2	----------
____	99	Other (specify)	☐	☐	1	----------
			☐	☐	2	----------

Please report medication(s) as specified in the protocol and fill in the **Medication** section.

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__|.|__| °C → Route : ☐ Axillary ☐ Rectal

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes ☐ No

STOOL SAMPLE (only for a subset)

Has a stool sample been taken on the day of administration? ☐ Yes* ☐ No ☐ NA

Has a post vaccination stool sample been taken on day 7 after administration? ☐ Yes* ☐ No ☐ NA

→ * please fill the stools collection section (Interim analysis after Visit 3) if any stools have been collected.

FEEDINGS

Is the child fed with :
- ☐ breast milk
- ☐ infant formula
- ☐ both

Did the child :
- ☐ receive no food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
- ☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
- ☐ receive food within 1 hour prior to vaccination but not 30 minutes after vaccination ?
- ☐ receive food within 30 minutes after vaccination but not 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 1** **DOSE 1**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / site** **Route**	**Has the study vaccine been administered According to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please specify (*)*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes
☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	Please fill the **GE Episodes** Section (Interim analysis after Visit 3)	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0 1 2 3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 2

4 months of age

(49 – 83 days after Visit 1)

DOSE 2

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the **Contraindications** as specified in the protocol.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected.

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 2**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 1 until visit 2 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections (Interim analysis after Visit 3)

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary
☐ Rectal

LABORATORY TESTS (only for a subset)

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes
☐ No ☐ NA

STOOL SAMPLE (only for a subset)

Has a stool sample been taken on the day of administration? ☐ Yes*
☐ No ☐ NA

Has a post vaccination stool sample been taken on day 7 after administration? ☐ Yes*
☐ No ☐ NA

→ * please fill the stools collection section (Interim analysis after Visit 3) if any stools have been collected.

FEEDINGS

Is the child fed with : ☐ breast milk
☐ infant formula
☐ both

Did the child :
☐ receive no food within 1 hour prior to vaccination <u>and</u> within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination <u>but not</u> 30 minutes after vaccination ?
☐ receive food within 30 minutes after vaccination <u>but not</u> 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 2** **DOSE 2**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / site** **Route**	**Has the study vaccine been administered According to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please specify (*)*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes
☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

Protocol 444563/006

DOSE 2

Subject Number |__|__|__|__|__|

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	Please fill the **GE Episodes** Section (Interim analysis after Visit 3)	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0 1 2 3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 3

6 MONTHS OF AGE

(49 – 83 days after Visit 2)

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the **Contraindications** as specified in the protocol.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected.

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 3**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 2 until visit 3 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections (Interim analysis after Visit 3)

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary ☐ Rectal

LABORATORY TESTS (only for a subset)

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes ☐ No ☐ NA

STOOLS

COLLECTION

INTERIM ANALYSIS

AFTER VISIT 3

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS AFTER VISIT 3**		|__|__|__|__|__|

STOOLS COLLECTION

STOOLS 1	STOOLS 2	STOOLS 3
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 4	**STOOLS 5**	**STOOLS 6**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 7	**STOOLS 8**	**STOOLS 9**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 10	**STOOLS 11**	**STOOLS 12**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 13	**STOOLS 14**	**STOOLS 15**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 16	**STOOLS 17**	**STOOLS 18**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS AFTER VISIT 3**		|__|__|__|__|__|

STOOLS COLLECTION

STOOLS 19	STOOLS 20	STOOLS 21
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 22	**STOOLS 23**	**STOOLS 24**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 25	**STOOLS 26**	**STOOLS 27**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 28	**STOOLS 29**	**STOOLS 30**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 31	**STOOLS 32**	**STOOLS 33**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 34	**STOOLS 35**	**STOOLS 36**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min

GASTROENTERITIS EPISODES

INTERIM ANALYSIS AFTER VISIT 3

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS AFTER VISIT 3**		|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample Taken**
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS AFTER VISIT 3**		|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample Taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS AFTER VISIT 3**		|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample Taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

CONCOMITANT VACCINATION

INTERIM ANALYSIS AFTER VISIT 3

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS AFTER VISIT 3**		|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administered at **ANY time since birth** ?

☐ No
☐ Yes, please record concomitant vaccination with trade name and / or generic name, and vaccine administration date.

Trade / Generic Name	**Administration date** day month year
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	

MEDICATION

INTERIM ANALYSIS
AFTER VISIT 3

MEDICATION ROUTE

CODE	LABEL
EXT	External
ID	Intradermal
IH	Inhalation
IM	Intramuscular
IR	Intraarticular
IT	Intrathecal
IV	Intravenous
NA	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS AFTER VISIT 3**		|__|__|__|__|__|

MEDICATION

→Any immunosuppressants or other immune-modifying drugs or treatments administered at ANY time during the period starting 30 days prior to the first dose of investigational vaccine and ending at Visit 3 must be recorded with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment. Any antibiotics administered within 7 days preceding each investigational vaccine/placebo administration and during the first 7 days after each investigational vaccine/placebo administration and any antipyretics administered at ANY time during the period starting 30 days prior to the first dose of investigational vaccine and ending one month (minimum 30 days) after the last dose of investigational vaccine/placebo must be recorded with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment.

→Any other concomitant medication administered prophylactically in anticipation of reaction to the vaccination must also be recorded with trade name and/or generic name of the medication, total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'

Have any of the above mentioned medications/treatments been administered during study period?

☐ No

☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or check box if continuing at end of study day month year	
	☐ Prophylactic			Start: |__|__||__|__|__||__|__|__|__| End: |__|__||__|__|__||__|__|__|__|	☐
For *SB*					
	☐ Prophylactic			Start: |__|__||__|__|__||__|__|__|__| End: |__|__||__|__|__||__|__|__|__|	☐
For *SB*					
	☐ Prophylactic			Start: |__|__||__|__|__||__|__|__|__| End: |__|__||__|__|__||__|__|__|__|	☐
For *SB*					
	☐ Prophylactic			Start: |__|__||__|__|__||__|__|__|__| End: |__|__||__|__|__||__|__|__|__|	☐
For *SB*					
	☐ Prophylactic			Start: |__|__||__|__|__||__|__|__|__| End: |__|__||__|__|__||__|__|__|__|	☐
For *SB*					
	☐ Prophylactic			Start: |__|__||__|__|__||__|__|__|__| End: |__|__||__|__|__||__|__|__|__|	☐
For *SB*					
	☐ Prophylactic			Start: |__|__||__|__|__||__|__|__|__| End: |__|__||__|__|__||__|__|__|__|	☐
For *SB*					

NON-SERIOUS ADVERSE EVENTS

INTERIM ANALYSIS AFTER VISIT 3

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS AFTER VISIT 3**		|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS

(Please report all **serious adverse events** only on the **Serious Adverse Event (SAE)** form).

Has any **non-serious adverse events** occurred within **one month (minimum 30 days)** post-vaccination, excluding those recorded on the **Solicited Adverse Events** pages ?
☐ No
☐ Yes, please complete the following table.

AE No.	**AE.1**	**AE.2**	**AE.3**
Description	----------	----------	----------
	☐ Local (injection sites) ☐ General (non injection site)	☐ Local (injection sites) ☐ General (non injection site)	☐ Local (injection sites) ☐ General (non injection site)
For SB			
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3
Causality In your opinion, did the vaccine possibly contribute to this AE ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Outcome	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at study conclusion (interim phase) ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at study conclusion (interim phase) ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at study conclusion (interim phase) ☐ 4 Died ☐ 5 Unknown

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS AFTER VISIT 3**		|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS (continued)

.

AE No.	**AE.4**	**AE.5**	**AE.6**
Description	----------	----------	----------
	☐ Local (injection sites) ☐ General (non injection site)	☐ Local (injection sites) ☐ General (non injection site)	☐ Local (injection sites) ☐ General (non injection site)
For SB			
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3
Causality In your opinion, did the vaccine possibly contribute to this AE ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Outcome	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at study conclusion (interim phase) ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at study conclusion (interim phase) ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at study conclusion (interim phase) ☐ 4 Died ☐ 5 Unknown

SERIOUS ADVERSE EVENT

INTERIM ANALYSIS AFTER VISIT 3

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EVENT (SAE)

SAE's MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

1. **COMPLETE THE SAE PAGES OPPOSITE.**
   Please complete these page as fully and accurately as possible in order to minimize the time you spend dealing with data queries.

   If the SAE is still ongoing at the time reporting, please leave "Outcome" blank and update it later.

2. **PLEASE ENSURE THAT ALL INFORMATION ON THE SAE PAGES IS CONSISTENT WITH THE FOLLOWING OTHER CRF PAGES.**
   - Demographics
   - General Medical History / Physical Examination
   - Vaccine Administration page(s) (for doses administered)
   - Medication
   - Concomitant Vaccination

3. **SIGN AND DATE THE SAE PAGES 2 (AND 3). COMPLETE PAGE 3 OF THE SAE FORM IF NEEDED ONLY.**

4. **PHOTOCOPY THE SAE PAGES (DO NOT SEPARATE THE NCR PAGES) AND FAX THE COPY OF THE SAE PAGES TO:**
   → The study contact
   (see Investigator Site File for appropriate fax number).

   → If no photocopier OR fax is available, please telephone to the study contact.

5. **FOR ADDITIONAL INFORMATION, PLEASE CHECK THE "ADDITIONAL INFO" BOX AND FOLLOW THE PROCEDURE EXPLAINED AT POINT 4.**

Protocol	Center	Country	SB Receipt Date	Subject Number
444563/006	|__|__|__|		|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

SERIOUS ADVERSE EVENT (SAE)

INTERIM ANALYSIS AFTER VISIT 3

☐ **(1)** Initial report ☐ **(3)** Additional info
☐ **(2)** Additional info ☐ **(4)** Additional info

Subject Demography (1)

Initials: |__|__| First name |__|__| Family name

Date of birth: |__|__| |__|__|__| |__|__|__|__| day month year

Gender : ☐ Male ☐ Female

Adverse Event *(please print clearly)* (2)

Diagnosis (or signs and symptoms if not known)

_____

_____

_____

For SB

Date and time started : (3)
(Adverse event first symptoms) |__|__| day |__|__|__| month |__|__|__|__| year |__|__|:|__|__| hours min

Date and time stopped : (4)
(If ongoing please leave blank) |__|__| day |__|__|__| month |__|__|__|__| year |__|__|:|__|__| hours min

Intensity : (5)
(maximum)
☐ 1
☐ 2
☐ 3

In your opinion, did the vaccine possibly contribute to the SAE : (6)
☐ No
☐ Yes

Outcome : (7)
(maximum)
☐ 1 Recovered
☐ 2 Recovered with sequelae
☐ 3 Ongoing
☐ 4 Died

Action taken with respect to Study Vaccine (8)
☐ None
☐ Vaccination course postponed
☐ Vaccination course stopped

Events after further vaccination (9)
☐ Event reappeared
☐ Event did not reappear
☐ Unknown at this time
☐ Not applicable

♦ **Specify criteria for considering this as a Serious Adverse Event.** (10)
(mark all that apply).

1 ☐ Result in death
→ Autopsy ? ☐ No ☐ Yes
↓
Send autopsy report when available

2 ☐ Life threatening

3 ☐ Result in persistent or significant disability/incapacity

4 ☐ Requires in-patient hospitalization.
Admission date: |__|__| day |__|__|__| month |__|__|__|__| year
Discharge date: |__|__| day |__|__|__| month |__|__|__|__| year

5 ☐ Prolongation of existing hospitalization
Discharge date: |__|__| day |__|__|__| month |__|__|__|__| year r

6 ☐ Congenital anomaly / birth defect in the offspring of a study subject.

7 ☐ "Medically important" event- specify: _____

♦ **Other events (not SAE) to be reported in the same way:**
☐ Cancer

Other possible contributors: (11)
(mark all that apply)
☐ Medical history *(record in section 15)*
☐ Other medication *(record in section 14)*
☐ Protocol required procedure
☐ Other procedure
☐ Lack of efficacy
☐ Erroneous administration
☐ Other, specify : _____

(record additional information in section 19)

Was subject withdrawn due to this specific SAE ? (12)
☐ No
☐ Yes

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS AFTER VISIT 3**	**SAE (continued)**	|__|__|__|__|__|

Study vaccine Information **(13)**

Vaccine *(specify mixed or separate)*	Dose No	Lot No	Route / Site	Date
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|

Concomitant medication / vaccination that could have contributed to this SAE **(14)**

Drug / vaccine	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Relevant intercurrent illness & medical history that could have contributed to this SAE **(15)**
(Including allergies)

Condition :	Still present? : No ☐ Yes ☐
Condition :	Still present? : No ☐ Yes ☐

Drug(s) used to treat this SAE **(16)**

Drug	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Surgical treatment for this SAE *(please specify)* **(17)**

Description *(provide a brief narrative description of the SAE including relevant diagnostic findings, lab data & evolution of the events etc…)* **(18)**

Investigator signature Date :	(1) |__|__| |__|__|__| |__|__|__|__| day month year	(2) |__|__| |__|__|__| |__|__|__|__| day month year	(3) |__|__| |__|__|__| |__|__|__|__| day month year	(4) |__|__| |__|__|__| |__|__|__|__| day month year
Please PRINT name:				

	Signature	*Please PRINT name*	*Date*
CDM:			|__|__| |__|__|__| |__|__|__|__| day month year

AEGIS Number : |__|__|__|__|__|__|__|__|__|__| - |__|__|

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS AFTER VISIT 3**	**SAE (continued)**	|__|__|__|__|__|

Study vaccine Information **(13)**

Investigator signature Date :	(1) |__| |___| |____| day month year	(2) |__| |___| |____| day month year	(3) |__| |___| |____| day month year	(4) |__| |___| |____| day month year
Please PRINT name:				

	Signature	*Please PRINT name*	*Date*
CDM:			|__| |___| |____| day month year

AEGIS Number : |______| - |___|

VISIT 4

1 YEAR OF AGE

(160 – 200 days after Visit 3)

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

CONCOMITANT VACCINATION

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected.

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 4**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from visit 3 until visit 4 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ?

☐ Yes
☐ No

STOOLS COLLECTION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STOOLS COLLECTION

STOOLS 1	STOOLS 2	STOOLS 3
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 4	**STOOLS 5**	**STOOLS 6**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 7	**STOOLS 8**	**STOOLS 9**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 10	**STOOLS 11**	**STOOLS 12**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 13	**STOOLS 14**	**STOOLS 15**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 16	**STOOLS 17**	**STOOLS 18**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STOOLS COLLECTION (continued)

STOOLS 19	STOOLS 20	STOOLS 21
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 22	**STOOLS 23**	**STOOLS 24**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 25	**STOOLS 26**	**STOOLS 27**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 28	**STOOLS 29**	**STOOLS 30**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 31	**STOOLS 32**	**STOOLS 33**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 34	**STOOLS 35**	**STOOLS 36**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min

GASTROENTERITIS EPISODES

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample Taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample Taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample Taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes

CONCOMITANT VACCINATION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administered at **ANY time between Visit 3 and Visit 4** ?

☐ No

☐ Yes, please record concomitant vaccination with trade name and / or generic name, and vaccine administration date.

Trade / Generic Name	**Administration date** day month year
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	
	|__|__||__|__|__||__|__|__|__|
For SB	

SERIOUS ADVERSE EVENT

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EVENT (SAE)

SAE's MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS

1. **COMPLETE THE SAE PAGES OPPOSITE.**
   Please complete these page as fully and accurately as possible in order to minimize the time you spend dealing with data queries.

   If the SAE is still ongoing at the time reporting, please leave "Outcome" blank and update it later.

2. **PLEASE ENSURE THAT ALL INFORMATION ON THE SAE PAGES IS CONSISTENT WITH THE FOLLOWING OTHER CRF PAGES.**
   - Demographics
   - General Medical History / Physical Examination
   - Vaccine Administration page(s) (for doses administered)
   - Medication
   - Concomitant Vaccination

3. **SIGN AND DATE THE SAE PAGES 2 (AND 3). COMPLETE PAGE 3 OF THE SAE FORM IF NEEDED ONLY.**

4. **PHOTOCOPY THE SAE PAGES (DO NOT SEPARATE THE NCR PAGES) AND FAX THE COPY OF THE SAE PAGES TO:**
   → The study contact
   (see Investigator Site File for appropriate fax number).

   → If no photocopier OR fax is available, please telephone to the study contact.

5. **FOR ADDITIONAL INFORMATION, PLEASE CHECK THE "ADDITIONAL INFO" BOX AND FOLLOW THE PROCEDURE EXPLAINED AT POINT 4.**

Protocol	Center	Country	SB Receipt Date	Subject Number
444563/006	|__|__|__|		|__|__| |__|__|__| |__|__|__|__| (day month year)	|__|__|__|__|__|

SERIOUS ADVERSE EVENT (SAE)

☐ **(1)** Initial report ☐ **(3)** Additional info
☐ **(2)** Additional info ☐ **(4)** Additional info

Subject Demography

Initials: \|__\|__\| \|__\|__\| (1)
First name Family name

Date of birth: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

Gender : ☐ Male ☐ Female

Adverse Event *(please print clearly)*

Diagnosis (or signs and symptoms if not known) (2)

_____

_____

_____

For SB

Date and time started : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\| (3)
(Adverse event first symptoms) day month year hours min

Date and time stopped : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\| (4)
(If ongoing please leave blank) day month year hours min

Intensity : ☐ 1 (5)
(maximum) ☐ 2
☐ 3

In your opinion, did the vaccine possibly contribute to the SAE : ☐ No ☐ Yes (6)

Outcome : ☐ 1 Recovered (7)
(maximum) ☐ 2 Recovered with sequelae
☐ 3 Ongoing
☐ 4 Died

Action taken with respect to Study Vaccine ☐ None (8)
☐ Vaccination course postponed
☐ Vaccination course stopped

Events after further vaccination ☐ Event reappeared (9)
☐ Event did not reappear
☐ Unknown at this time
☐ Not applicable

♦ **Specify criteria for considering this as a Serious Adverse Event.** (10)
(mark all that apply).

1 ☐ Result in death
→ Autopsy ? ☐ No ☐ Yes
↓
Send autopsy report when available

2 ☐ Life threatening

3 ☐ Result in persistent or significant disability/incapacity

4 ☐ Requires in-patient hospitalization.
Admission date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

5 ☐ Prolongation of existing hospitalization
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year r

6 ☐ Congenital anomaly / birth defect in the offspring of a study subject.

7 ☐ "Medically important" event- specify:
_____

♦ **Other events (not SAE) to be reported in the same way:**
☐ Cancer

Other possible contributors: (11)
(mark all that apply)
☐ Medical history *(record in section 15)*
☐ Other medication *(record in section 14)*
☐ Protocol required procedure
☐ Other procedure
☐ Lack of efficacy
☐ Erroneous administration
☐ Other, specify : _____
(record additional information in section 19)

Was subject withdrawn due to this specific SAE ? ☐ No ☐ Yes (12)

Protocol				Subject Number
444563/006			**SAE (continued)**	|__|__|__|__|__|

Study vaccine Information **(13)**

Vaccine *(specify mixed or separate)*	Dose No	Lot No	Route / Site	Date
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|

Concomitant medication / vaccination that could have contributed to this SAE **(14)**

Drug / vaccine	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Relevant intercurrent illness & medical history that could have contributed to this SAE **(15)**
(Including allergies)

Condition :	Still present? : No ☐ Yes ☐
Condition :	Still present? : No ☐ Yes ☐

Drug(s) used to treat this SAE **(16)**

Drug	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Surgical treatment for this SAE *(please specify)* **(17)**

Description *(provide a brief narrative description of the SAE including relevant diagnostic findings, lab data & evolution of the events etc…)* **(18)**

Investigator signature Date :	(1) |__|__| |__|__|__| |__|__|__|__| day month year	(2) |__|__| |__|__|__| |__|__|__|__| day month year	(3) |__|__| |__|__|__| |__|__|__|__| day month year	(4) |__|__| |__|__|__| |__|__|__|__| day month year
Please PRINT name:				

	Signature	*Please PRINT name*	*Date*
CDM:			|__|__| |__|__|__| |__|__|__|__| day month year

AEGIS Number : |__|__|__|__|__|__|__|__|__|__| - |__|__|

Protocol				Subject Number
444563/006			**SAE (continued)**	|__|__|__|__|__|

Study vaccine Information **(13)**

Investigator signature Date :	(1) |__|__| |__|__|__|__| day month year	(2) |__|__| |__|__|__|__| day month year	(3) |__|__| |__|__|__|__| day month year	(4) |__|__| |__|__|__|__| day month year
Please PRINT name:				

	Signature	*Please PRINT name*	*Date*
CDM:			|__|__| |__|__|__|__| |__|__|__|__| day month year

AEGIS Number : |__|__|__|__|__|__|__|__|__|__| - |__|__|

STUDY CONCLUSION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STUDY CONCLUSION

Has the code been broken?

☐ No
☐ Yes

Did any elimination criteria become applicable during the study?

☐ No
☐ Yes, please specify: _____

Has the subject dropped out of the study?
(a drop out is a subject who did not come back for the concluding visit foreseen in the protocol.)

☐ No
☐ Yes, please mark the **ONE most appropriate** category for drop out.

- ☐ (SAE) Serious adverse event (complete the **Serious Adverse Event form**).
- ☐ (AEX) Non-Serious adverse event (complete the **Non-serious Adverse Event form**).

  Please specify AE N°: _____
- ☐ (PTV) Protocol violation, please specify : _____
- ☐ (CWS) Consent withdrawal, not due to an adverse event.
- ☐ (MIG) Migrated / moved from the study area
- ☐ (LFU) Lost to follow-up.
- ☐ (OTH) Other, please specify : _____

Date of last contact : |__|__| |__|__|__| |__|__|__|__|
day month year

Was the subject in good condition at date of last contact?

☐ No, please give details within the **Adverse Events section.**
☐ Yes

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this case report form, the Non-Serious Adverse Events and Serious Adverse Event sections including any laboratory data (if appropriate) and that all information is complete and accurate.

Date of last contact : |__|__| |__|__|__| |__|__|__|__| Investigator signature :

SmithKline Beecham Biologicals s.a.

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	**SOLICITED SYMPTOMS**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose
- **0**: Normal
- **1**: Cough/runny nose which is easily tolerated
- **2**: Cough/runny nose which interferes with daily activity
- **3**: Cough/runny nose which prevents daily activity

Irritability / fussiness:
- **0**: Behavior as usual
- **1**: Crying more than usual / no effect on normal activity
- **2**: Crying more than usual / interferes with normal activity
- **3**: Crying that cannot be comforted/ prevents normal activity

Loss of appetite:
- 0: Normal
- 1: Eating less than usual / no effect on normal activity
- 2: Eating less than usual / interferes with normal activity
- 3: Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given.

SOLICITED SYMPTOMS	Day 0	Day 1 evening	Day 2 evening	Day 3 evening	Day 4 evening	Day 5 evening	Day 6 evening	Day 7 evening	Day 8 evening	Day 9 evening	Day 10 evening	Day 11 evening	Day 12 evening	Day 13 evening	Day 14 evening	Ongoing after day 14?	Date of last day of symptoms day month year
Date:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____		
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Irritability/fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	**if ongoing after day 14, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET**
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

MEDICATION FOR DIARRHEA
- ☐ None
- ☐ Oral rehydration
- ☐ Other, please specify----------

HOSPITALISATION FOR DIARRHEA :
- ☐ No
- ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__||__|__|__||__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 14**	**DOSE 1**	|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea.

SOLICITED GASTROENTERITIS SYMPTOMS	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__|__|__|__|__|__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

SmithKline Beecham Biologicals s.a.

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**GASTROENTERITIS EPISODES**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS is defined as presence of diarrhea
DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	**OTHER GENERAL SYMPTOMS AND MEDICATION**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

INTENSITY:

Other general symptoms:

1: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse event which prevents normal, everyday activities. (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten / a day-care center and would cause the parents / guardians to seek medical advice).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis symptoms) Please give details below	Intensity	Start date day month year	End date or check box if continuing day month year	
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐

MEDICATION Please fill in below if any medication has been taken since the vaccination **(excluding oral rehydration)**		Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
Trade / generic name	Reason				
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**SOLICITED SYMPTOMS**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose
- **0**: Normal
- **1**: Cough/runny nose which is easily tolerated
- **2**: Cough/runny nose which interferes with daily activity
- **3**: Cough/runny nose which prevents daily activity

Irritability / fussiness:
- **0**: Behavior as usual
- **1**: Crying more than usual / no effect on normal activity
- **2**: Crying more than usual / interferes with normal activity
- **3**: Crying that cannot be comforted/ prevents normal activity

Loss of appetite:
- 0: Normal
- 1: Eating less than usual / no effect on normal activity
- 2: Eating less than usual / interferes with normal activity
- 3: Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given.

SOLICITED SYMPTOMS	Day 0	Day 1 evening	Day 2 evening	Day 3 evening	Day 4 evening	Day 5 evening	Day 6 evening	Day 7 evening	Day 8 evening	Day 9 evening	Day 10 evening	Day 11 evening	Day 12 evening	Day 13 evening	Day 14 evening	Ongoing after day 14?	Date of last day of symptoms day month year
Date:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____		
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Irritability/fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	**if ongoing after day 14, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET**
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

MEDICATION FOR DIARRHEA
- ☐ None
- ☐ Oral rehydration
- ☐ Other, please specify----------

HOSPITALISATION FOR DIARRHEA :
- ☐ No
- ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__|__|__|__|__|__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 14**	**DOSE 2**	|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea.

SOLICITED GASTROENTERITIS SYMPTOMS	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__|__|__|__|__|__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

SmithKline Beecham Biologicals s.a.

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**GASTROENTERITIS EPISODES**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS is defined as presence of diarrhea.
DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episode of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and/or vomiting and record whether medical treatment was given

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**OTHER GENERAL SYMPTOMS AND MEDICATION**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

INTENSITY:

Other general symptoms:

1: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse event which prevents normal, everyday activities. (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten / a day-care center and would cause the parents / guardians to seek medical advice).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis symptoms) Please give details below	Intensity	Start date day month year	End date or check box if continuing day month year	
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
	|__|	|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐

MEDICATION Please fill in below if any medication has been taken since the vaccination **(excluding oral rehydration)**		Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
Trade / generic name	Reason				
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐
			|__|__||__|__|__||__|__|__|__|	|__|__||__|__|__||__|__|__|__|	☐

Center	Subject identification	Subject Number
|__|__|__|	|__|__| First name |__|__| Family name	|__|__|__|__|__|

CONFIDENTIAL

WORKBOOK

444563/006 (Rota-006)
Amendment 1

GlaxoSmithKline

Rue de l'institut 89, B – 1330 Rixensart, Belgium
Tel: [redacted] Fax: [redacted]

Version 11.2
Date : March 7, 2001

GENERAL INSTRUCTIONS

Print clearly in **CAPITAL LETTERS** using a **black** fountain or ball-point pen and press firmly so that all copies are legible. Insert the writing board beneath all copies of the form being completed. Fill in the subject number on every page and answer all questions except where otherwise indicated.

Do not write in shaded areas which are qualified **"For GSK"**. Information written in these areas **are not the responsibility of the investigator**.
For each subject's **INITIALS**, please enter the first two letters of the first name and the first two letters of the family name.

ABBREVIATIONS: Abbreviations for medical conditions, clinical events or drug names should not be used. Units and route of administration of medication may be abbreviated. NA: not applicable.

IMPORTANT: Errors should be crossed out with a single line and the alteration made as near to the original as possible.
All alterations must be printed, initialled and dated by the investigator or authorized staff.

DATE

Use the following three-letter abbreviations for each month:

January	=	JAN
February	=	FEB
March	=	MAR
April	=	APR
May	=	MAY
June	=	JUN
July	=	JUL
August	=	AUG
September	=	SEP
October	=	OCT
November	=	NOV
December	=	DEC

Example : |0|1| |J|A|N| |2|0|0|0| = 1st January 2000
day month year

TIME

Unless specified otherwise, use the 24 hour clock :

Example: |1|5| : |3|0| = 3.30 p.m.
hours min

The **Medication** section, the **Concomitant Vaccination** section, the **Non-Serious Adverse Events** section and the **Serious Adverse Event (SAE)** form must be checked for final assessment at the end of the study.

For all subjects enrolled, please complete the **Conclusion after the first rotavirus season and the Study conclusion** forms.

ADVERSE EVENT DEFINITIONS

INTENSITY FOR SOLICITED SYMPTOMS

Cough/runny nose

0 : Normal
1 : Cough/runny nose which is easily tolerated
2 : Cough/runny nose which interferes with daily activity
3 : Cough/runny nose which prevents daily activity

Irritability/Fussiness

0 : Behavior as usual
1 : Crying more than usual / no effect on normal activity
2 : Crying more than usual / interferes with normal activity
3 : Crying that cannot be comforted / prevents normal activity

Loss of appetite

0 : Normal
1 : Eating less than usual / no effect on normal activity
2 : Eating less than usual / interferes with normal activity
3 : Not eating at all

GASTROENTERITIS EPISODES

Any diarrhea defined as three or more looser than normal stools within a day.

INTENSITY FOR NON-SOLICITED SYMPTOMS

0 : No adverse event.
1 : An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 : An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3 : An adverse event which prevents normal, everyday activities
(In a young child, such an adverse event would, for example, prevent attendance at school/kindergarten/ a day-care center and would cause the parents/guardians to seek medical advice).

ADVERSE EVENT DEFINITIONS

CAUSALITY

In your opinion, did the vaccine(s) possibly contribute to the adverse event?

NO : The adverse event is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the adverse event.

YES: There is a reasonable possibility that the vaccine contributed to the adverse event.

OUTCOME

1 : Recovered
2 : Recovered with sequelae
3 : Ongoing at study conclusion active phase or safety follow-up (whichever is applicable)
4 : Died
5 : Unknown

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that:

1 : results in death
2 : is life threatening
3 : results in persistent or significant disability / incapacity
4 : requires in-patient hospitalization
5 : prolongation of existing hospitalization
6 : is a congenital anomaly / birth defect in the offspring of a study subject
7 : In addition, important medical events that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not results in hospitalization; or development of drug dependency or drug abuse).

For each serious adverse event, please fill in the **Serious Adverse Event (SAE)** form and contact GlaxoSmithKline within 24 hours (one calendar day).

Although not considered as 'serious adverse events', cancers must be reported in the same way as serious adverse events.

SmithKline Beecham

FLOW SHEET

Age	**2 months**	**4 months**	**6 months**	**1 year**
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4**
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 MO 4**	**Post vacc 2 MO 10**
Informed consent	•			
Medical history	•			
Check of inclusion criteria	•			
Check of exclusion criteria	•			
Check of elimination criteria		•	•	•
Check of contraindications	•	•	•	
Physical examination	•	•	•	•
Pre-vaccination body temperature	•	•	•	
Measure/record height and weight	•	•	•	•
Blood sampling	• (1 ml of blood)	• (1 ml of blood in a subset)	• (3 mls of blood in a subset)	• (3 mls of blood in a subset, 1 ml for all others)
Randomisation	•			
Stool samples will be collected from a subset (N = 400) on the day of administration of dose 1 and dose 2 and on day 7 following each dose.	•	•		
Study Vaccine	•	•		
Routine Vaccination	•	•	•	
Daily post-vaccination recording of solicited symptoms (days 0–14) by parents/guardians	•	•		
Collection of stool samples	•	•	•	•
Recording of solicited symptoms, non serious adverse events within 42 days after dose 1 and dose 2, by investigator		•	•	
Contact (field visit) every week.	◊	◊	◊	◊
Return of GE diary	•	•	•	•
GE diary transcription		•	•	•
Documentation of routine EPI vaccines	•	•	•	•
Recording medication	•	•	•	
Reporting of Serious Adverse Events occurring throughout the study period	•	•	•	•
Study Conclusion				•

◊ is used to indicate a study procedure which does not require documentation in the individual eCRFs.

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed. These intervals determine a subject's evaluability in the according to protocol analyses.

Intervals between study visits*

Interval	Size of interval
1 (Visit 1→Visit 2)	49 - 83 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→Visit 4)	160 - 200 days

*The date of the previous visit is the reference date.

VISIT 1

6 to 12 weeks of age

DOSE 1

Informed Consent has to be obtained prior to any study procedure

ELIGIBILITY CHECKLIST

INCLUSION CRITERIA

All subjects enrolled must satisfy the following criteria at study entry :

1. A male or female child between, and including 6 and 12 weeks (42-90 days) of age at the time of the first vaccination.
2. Free of obvious health problems as established by medical history and clinical examination before entering into the study.
3. Written informed consent obtained from the parents or guardians of the subject.
4. Born after a gestation period (between 36 and 42 weeks) or a birth weight > 2000g.

EXCLUSION CRITERIA FOR ENROLMENT

The following criteria should be checked at the time of study entry. If any apply at the time of study entry, the subject must not be included in the study :

5. Use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the study vaccine or placebo or planned use during the study period.
6. Planned administration of a vaccine (including routine pediatric vaccines) not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.
7. Planned administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
8. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth. (Topical steroids are allowed.)
9. History of diphtheria, tetanus, pertussis, Hib disease and/ or hepatitis B.
10. Previous vaccination against diphtheria, tetanus, pertussis, and/or *Haemophilus influenzae* type b.
11. Use of antibiotics within 7 days preceding dose 1 (Warrants deferral of vaccination pending recovery of the subject).
12. Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the GI tract or other serious medical condition as determined by the investigator.
13. Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
14. History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.
15. Acute disease at time of enrollment. (Acute disease is defined as the presence of moderate or severe illness with or without fever i.e. temperature ≥ 37.5°C as measured by an axillary thermometer or ≥ 38.0°C as measured by a rectal thermometer). A temperature greater than or equal to these cut-off warrants deferral of the vaccination pending recovery of the subject.
16. Gastroenteritis within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).
17. Household contact with an immunosuppressed individual or pregnant women.
18. Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
19. Previous confirmed occurrence of rotavirus gastroenteritis.

ELIMINATION CRITERIA TO BE CHECKED AT VISITS 2 AND 3

The following criteria should be checked at Visits 2 and 3. If any become applicable during the study, the subject will not be required to discontinue the study but may be eliminated from the according-to-prtocol analysis.

- Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
- Use of antibiotics during the period starting from 7 days before dose 1 and 2 and ending 7 days after.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
- Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of vaccine(s) and ending 14 days after.
- Administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
- Administration of immunoglobulins and/or any blood products during the study period.
- Confirmed immunosuppressive or immunodeficient condition, including HIV.

ELIMINATION CRITERIA DURING THE STUDY FROM VISIT 3 TO VISIT 4

The following criteria should be checked at visit 4. If any become applicable during the study, the subject may be eliminated from the according-to-protocol analysis.

- Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
- Administration of immunoglobulins and/or any blood products during the study period.
- Confirmed immunosuppressive or immunodeficient condition, including HIV.

Contraindications and precautions for further doses

SB Biologicals' HRV vaccine or placebo:

The following adverse events constitute absolute contraindications to further administration of human rotavirus vaccine or placebo; if any of these adverse events occur during the study, the subject must not receive additional doses of vaccine or placebo but may continue other study procedures at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event :

- Hypersensitivity reaction due to the vaccine.
- Intussusception

The following adverse events constitute contraindications to administration of human rotavirus vaccine or placebo at a given point in time; if any one of these adverse events occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol or withdrawn at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event.

- Axillary/rectal temperature ≥37.5°C/38.0°C
- Gastroenteritis within 7 days preceding the study vaccine administration

DTPw-HB+Hib vaccine:

The following adverse events constitute absolute contraindications or precautions to further administration of DTPw-HB+Hib vaccine; if any of these adverse events occurs during the study, the subject must be withdrawn and must be followed until resolution of the event, as with any adverse event:

Absolute contraindications:

- Known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B or Hib vaccines.
- Encephalopathy (not due to another identifiable cause). This is defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, and/or generalized or focal seizures that persist more than a few hours, with failure to recover within 24 hours. Even though causation by DTP-containing vaccine cannot be established, no subsequent doses of pertussis vaccine should be given.

Precautions:

If the following adverse events occur in temporal relation to DTPw-HB+Hib vaccine administration, the decision to administer additional doses of DTPw-HB+Hib vaccine should be carefully considered:

- Fever ≥ 40.5°C/≥ 40.0°C (rectal/axillary temperature) within 48 hours of vaccination not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting >3 hours, occurring within 48 hours of vaccination.
- Seizures with or without fever occurring within 3 days of vaccination.

Protocol	Center	Visit	Date of visit	Subject Number
444563/006	|__|__|__|	**VISIT 1**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date : |__|__| |__|__|__| |__|__|__|__|
day month year

DEMOGRAPHICS

Subject initials : |__|__| |__|__|
First name Family name

Date of birth : |__|__| |__|__|__| |__|__|__|__|
day month year

Gender : ☐ Male
☐ Female

Race : ☐ (WH) White
☐ (BL) Black
☐ (OR) Oriental
☐ (OT) Other, please specify: _____

Height : |__|__|__| cm

Weight : |__|__|__| . |__| kg

Is the subject eligible for the study, according to the criteria listed hereby ?

☐ Yes
☐ No, please give the corresponding criterion number(s) : _____

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

GENERAL MEDICAL HISTORY / PHYSICAL EXAMINATION

Are you aware of any pre-existing conditions or signs and/or symptoms present in the subject prior to the start of the study ?

☐ No

☐ Yes, please check appropriate box(es) and give diagnosis

			PAST	CURRENT		DIAGNOSIS
____	10	Cutaneous	☐	☐	1	----------
			☐	☐	2	----------
____	5	Eyes	☐	☐	1	----------
			☐	☐	2	----------
____	6	Ears-nose-throat	☐	☐	1	----------
			☐	☐	2	----------
____	2	Cardiovascular	☐	☐	1	----------
			☐	☐	2	----------
____	3	Respiratory	☐	☐	1	----------
			☐	☐	2	----------
____	1	Gastrointestinal	☐	☐	1	----------
			☐	☐	2	----------
____	7	Musculoskeletal	☐	☐	1	----------
			☐	☐	2	----------
____	8	Neurological	☐	☐	1	----------
			☐	☐	2	----------
____	12	Genitourinary	☐	☐	1	----------
			☐	☐	2	----------
____	11	Haematology	☐	☐	1	----------
			☐	☐	2	----------
____	4	Allergies	☐	☐	1	----------
			☐	☐	2	----------
____	9	Endocrine	☐	☐	1	----------
			☐	☐	2	----------
____	99	Other (specify)	☐	☐	1	----------
			☐	☐	2	----------

Please report medication(s) as specified in the protocol and fill in the **Medication** section.

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary ☐ Rectal

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes ☐ No

STOOL SAMPLE (only for a subset)

Has a stool sample been taken on the day of administration? ☐ Yes* ☐ No ☐ NA

Has a post vaccination stool sample been taken on day 7 after administration? ☐ Yes* ☐ No ☐ NA

→ *** please fill the stools collection section (Interim analysis) if any stools have been collected.**

FEEDINGS

Is the child fed with :
- ☐ breast milk
- ☐ infant formula
- ☐ both

Did the child :
- ☐ receive no food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
- ☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
- ☐ receive food within 1 hour prior to vaccination but not 30 minutes after vaccination ?
- ☐ receive food within 30 minutes after vaccination but not 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 1** **DOSE 1**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / site** **Route**	**Has the study vaccine been administered According to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please specify (*)*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes ☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	Please fill the **GE Episodes** Section (Interim analysis)	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0 1 2 3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 2

4 months of age

(49 – 83 days after Visit 1)

DOSE 2

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the **Contraindications** as specified in the protocol.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected.

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 2**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 1 until visit 2 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections (Interim analysis)

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary
☐ Rectal

LABORATORY TESTS (only for a subset)

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes
☐ No ☐ NA

STOOL SAMPLE (only for a subset)

Has a stool sample been taken on the day of administration? ☐ Yes*
☐ No ☐ NA

Has a post vaccination stool sample been taken on day 7 after administration? ☐ Yes*
☐ No ☐ NA

→ *** please fill the stools collection section (Interim analysis) if any stools have been collected.**

FEEDINGS

Is the child fed with : ☐ breast milk
☐ infant formula
☐ both

Did the child :
☐ receive no food within 1 hour prior to vaccination <u>and</u> within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination <u>but not</u> 30 minutes after vaccination ?
☐ receive food within 30 minutes after vaccination <u>but not</u> 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 2** **DOSE 2**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / site** **Route**	**Has the study vaccine been administered According to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please specify (*)*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes ☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	Please fill the **GE Episodes** Section (Interim analysis)	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0 1 2 3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 3

6 MONTHS OF AGE

(49 – 83 days after Visit 2)

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the **Contraindications** as specified in the protocol.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected.

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 3**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 2 until visit 3 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections (Interim analysis)

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary
☐ Rectal

LABORATORY TESTS (only for a subset)

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes
☐ No ☐ NA

STOOLS
COLLECTION
INTERIM ANALYSIS

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS**		|__|__|__|__|__|

STOOLS COLLECTION

STOOLS 1	STOOLS 2	STOOLS 3
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 4	**STOOLS 5**	**STOOLS 6**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 7	**STOOLS 8**	**STOOLS 9**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 10	**STOOLS 11**	**STOOLS 12**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 13	**STOOLS 14**	**STOOLS 15**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 16	**STOOLS 17**	**STOOLS 18**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS**		|__|__|__|__|__|

STOOLS COLLECTION

STOOLS 19	STOOLS 20	STOOLS 21
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 22	**STOOLS 23**	**STOOLS 24**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 25	**STOOLS 26**	**STOOLS 27**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 28	**STOOLS 29**	**STOOLS 30**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 31	**STOOLS 32**	**STOOLS 33**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 34	**STOOLS 35**	**STOOLS 36**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min

GASTROENTERITIS EPISODES

INTERIM ANALYSIS

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS**		|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample Taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS**		|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample Taken**
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS**		|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample Taken**
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

CONCOMITANT VACCINATION

INTERIM ANALYSIS

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS**		|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administered at **ANY time since birth** ?

☐ No
☐ Yes, please record concomitant vaccination with trade name and / or generic name, and vaccine administration date.

Trade / Generic Name	**Administration date** day month year
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	

MEDICATION

INTERIM ANALYSIS

GlaxoSmithKline

MEDICATION ROUTE

CODE	LABEL
EXT	External
ID	Intradermal
IH	Inhalation
IM	Intramuscular
IR	Intraarticular
IT	Intrathecal
IV	Intravenous
NA	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS**		|__|__|__|__|__|

MEDICATION

→Any immunosuppressants or other immune-modifying drugs or treatments administered at ANY time during the period starting 30 days prior to the first dose of investigational vaccine and ending at Visit 3 must be recorded with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment. Any antibiotics administered within 7 days preceding each investigational vaccine/placebo administration and during the first 7 days after each investigational vaccine/placebo administration and any antipyretics administered at ANY time during the period starting 30 days prior to the first dose of investigational vaccine and ending one month (minimum 30 days) after the last dose of investigational vaccine/placebo must be recorded with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment.

→Any other concomitant medication administered prophylactically in anticipation of reaction to the vaccination must also be recorded with trade name and/or generic name of the medication, total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'

Have any of the above mentioned medications/treatments been administered during study period?

☐ No

☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or check box if continuing at end of study day month year	
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					

NON-SERIOUS ADVERSE EVENTS

INTERIM ANALYSIS

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS**		|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS

(Please report all **serious adverse events** only on the **Serious Adverse Event (SAE)** form).

Has any **non-serious adverse events** occurred within **42 days after each vaccine administration** , excluding those recorded on the **Solicited Adverse Events** pages ?

☐ No
☐ Yes, please complete the following table.

AE No.	**AE.1**	**AE.2**	**AE.3**
Description	----------	----------	----------
	☐ Local (injection sites) ☐ General (non injection site)	☐ Local (injection sites) ☐ General (non injection site)	☐ Local (injection sites) ☐ General (non injection site)
For GSK			
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3
Causality In your opinion, did the vaccine possibly contribute to this AE ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Outcome	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at study conclusion (interim phase) ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at study conclusion (interim phase) ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at study conclusion (interim phase) ☐ 4 Died ☐ 5 Unknown

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS**		|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS (continued)

.

AE No.	**AE.4**	**AE.5**	**AE.6**
Description	----------	----------	----------
	☐ Local (injection sites) ☐ General (non injection site)	☐ Local (injection sites) ☐ General (non injection site)	☐ Local (injection sites) ☐ General (non injection site)
For GSK			
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3
Causality In your opinion, did the vaccine possibly contribute to this AE ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Outcome	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at study conclusion (interim phase) ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at study conclusion (interim phase) ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at study conclusion (interim phase) ☐ 4 Died ☐ 5 Unknown

SERIOUS ADVERSE EVENT

INTERIM ANALYSIS

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EVENT (SAE)

SAE's MUST BE REPORTED TO GLAXOSMITHKLINE WITHIN 24 HOURS

1. **COMPLETE THE SAE PAGES OPPOSITE.**

   Please complete these page as fully and accurately as possible in order to minimize the time you spend dealing with data queries.

   If the SAE is still ongoing at the time reporting, please leave "Outcome" blank and update it later.

2. **PLEASE ENSURE THAT ALL INFORMATION ON THE SAE PAGES IS CONSISTENT WITH THE FOLLOWING OTHER CRF PAGES.**

   - Demographics
   - General Medical History / Physical Examination
   - Vaccine Administration page(s) (for doses administered)
   - Medication
   - Concomitant Vaccination

3. **SIGN AND DATE THE SAE PAGES 2 (AND 3). COMPLETE PAGE 3 OF THE SAE FORM IF NEEDED ONLY.**

4. **PHOTOCOPY THE SAE PAGES (DO NOT SEPARATE THE NCR PAGES) AND FAX THE COPY OF THE SAE PAGES TO:**

   → The study contact
   (see Investigator Site File for appropriate fax number).

   → If no photocopier OR fax is available, please telephone to the study contact.

5. **FOR ADDITIONAL INFORMATION, PLEASE CHECK THE "ADDITIONAL INFO" BOX AND FOLLOW THE PROCEDURE EXPLAINED AT POINT 4.**

Protocol	Center	Country	GSK Receipt Date	Subject Number
444563/006	|__|__|__|		|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

SERIOUS ADVERSE EVENT (SAE) INTERIM ANALYSIS

☐ **(1)** Initial report ☐ **(3)** Additional info
☐ **(2)** Additional info ☐ **(4)** Additional info

Subject Demography (1)

Initials: \|__\|__\| First name \|__\|__\| Family name

Date of birth: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

Gender : ☐ Male ☐ Female

Adverse Event *(please print clearly)* (2)

Diagnosis (or signs and symptoms if not known)

_____

_____

_____

For GSK

(3)

Date and time started : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\|
(Adverse event first symptoms) day month year hours min

(4)

Date and time stopped : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\|
(If ongoing please leave blank) day month year hours min

Intensity : (5)
(maximum)
☐ 1
☐ 2
☐ 3

In your opinion, did the vaccine possibly contribute to the SAE : (6)
☐ No
☐ Yes

Outcome : (7)
(maximum)
☐ 1 Recovered
☐ 2 Recovered with sequelae
☐ 3 Ongoing
☐ 4 Died

Action taken with respect to Study Vaccine (8)
☐ None
☐ Vaccination course postponed
☐ Vaccination course stopped

Events after further vaccination (9)
☐ Event reappeared
☐ Event did not reappear
☐ Unknown at this time
☐ Not applicable

♦ **Specify criteria for considering this as a Serious Adverse Event.**
(mark all that apply).

1 ☐ Result in death
→ Autopsy ? ☐ No ☐ Yes
↓
Send autopsy report when available

2 ☐ Life threatening

3 ☐ Result in persistent or significant disability/incapacity

4 ☐ Requires in-patient hospitalization.
Admission date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

5 ☐ Prolongation of existing hospitalization
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year r

6 ☐ Congenital anomaly / birth defect in the offspring of a study subject.

7 ☐ "Medically important" event- specify:
_____

♦ **Other events (not SAE) to be reported in the same way:**
☐ Cancer

Other possible contributors: (11)
(mark all that apply)
☐ Medical history *(record in section 15)*
☐ Other medication *(record in section 14)*
☐ Protocol required procedure
☐ Other procedure
☐ Lack of efficacy
☐ Erroneous administration
☐ Other, specify : _____

(record additional information in section 19)

Was subject withdrawn due to this specific SAE ? (12)
☐ No
☐ Yes

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS**	**SAE (continued)**	|__|__|__|__|__|

Study vaccine Information **(13)**

Vaccine *(specify mixed or separate)*	Dose No	Lot No	Route / Site	Date
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|

Concomitant medication / vaccination that could have contributed to this SAE **(14)**

Drug / vaccine	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Relevant intercurrent illness & medical history that could have contributed to this SAE **(15)**
(Including allergies)

Condition :	Still present? : No ☐ Yes ☐
Condition :	Still present? : No ☐ Yes ☐

Drug(s) used to treat this SAE **(16)**

Drug	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Surgical treatment for this SAE *(please specify)* **(17)**

Description *(provide a brief narrative description of the SAE including relevant diagnostic findings, lab data & evolution of the events etc…)* **(18)**

Investigator signature Date :	(1) |__|__| |__|__|__|__| day month year	(2) |__|__| |__|__|__|__| day month year	(3) |__|__| |__|__|__|__| day month year	(4) |__|__| |__|__|__|__| day month year
Please PRINT name:				

	Signature	*Please PRINT name*	*Date*
CDM:			|__|__| |__|__|__|__| day month year

AEGIS Number : |__|__|__|__|__|__|__|__|__|__| - |__|__|

Protocol				Subject Number
444563/006		**INTERIM ANALYSIS**	**SAE (continued)**	|__|__|__|__|__|

Comments *(please provide further comments concerning the case)* **(19)**

Investigator signature Date :	(1) |__|__| |__|__|__|__| |__|__|__|__| day month year	(2) |__|__| |__|__|__|__| |__|__|__|__| day month year	(3) |__|__| |__|__|__|__| |__|__|__|__| day month year	(4) |__|__| |__|__|__|__| |__|__|__|__| day month year
Please PRINT name:				

	Signature	*Please PRINT name*	*Date*
CDM:			|__|__| |__|__|__|__| |__|__|__|__| day month year

AEGIS Number : |__|__|__|__|__|__|__|__|__|__| - |__|__|

VISIT 4

1 YEAR OF AGE

(160 – 200 days after Visit 3)

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

CONCOMITANT VACCINATION

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected.

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 4**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from visit 3 until visit 4 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ?

☐ Yes
☐ No

STOOLS COLLECTION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STOOLS COLLECTION

STOOLS 1	STOOLS 2	STOOLS 3
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 4	**STOOLS 5**	**STOOLS 6**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 7	**STOOLS 8**	**STOOLS 9**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 10	**STOOLS 11**	**STOOLS 12**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 13	**STOOLS 14**	**STOOLS 15**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min
STOOLS 16	**STOOLS 17**	**STOOLS 18**
Date : |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year **Time** : |__|__|: |__|__| hour min

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STOOLS COLLECTION (continued)

STOOLS 19	STOOLS 20	STOOLS 21
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 22	**STOOLS 23**	**STOOLS 24**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 25	**STOOLS 26**	**STOOLS 27**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 28	**STOOLS 29**	**STOOLS 30**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 31	**STOOLS 32**	**STOOLS 33**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 34	**STOOLS 35**	**STOOLS 36**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min

GASTROENTERITIS EPISODES

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample Taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample Taken**
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample Taken**
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__||__|__|__||__|__|__|__|	|__|	|__|	|__|__| . |__|	☐ not taken	☐ No ☐ Yes

CONCOMITANT VACCINATION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administered at **ANY time between Visit 3 and Visit 4** ?

☐ No

☐ Yes, please record concomitant vaccination with trade name and / or generic name, and vaccine administration date.

Trade / Generic Name	**Administration date** day month year
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	

SERIOUS ADVERSE EVENT

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EVENT (SAE)

SAE's MUST BE REPORTED TO GLAXOSMITHKLINE WITHIN 24 HOURS

1. **COMPLETE THE SAE PAGES OPPOSITE.**

   Please complete these page as fully and accurately as possible in order to minimize the time you spend dealing with data queries.

   If the SAE is still ongoing at the time reporting, please leave "Outcome" blank and update it later.

2. **PLEASE ENSURE THAT ALL INFORMATION ON THE SAE PAGES IS CONSISTENT WITH THE FOLLOWING OTHER CRF PAGES.**

   - Demographics
   - General Medical History / Physical Examination
   - Vaccine Administration page(s) (for doses administered)
   - Medication
   - Concomitant Vaccination

3. **SIGN AND DATE THE SAE PAGES 2 (AND 3). COMPLETE PAGE 3 OF THE SAE FORM IF NEEDED <u>ONLY</u>.**

4. **PHOTOCOPY THE SAE PAGES (DO NOT SEPARATE THE NCR PAGES) AND FAX THE COPY OF THE SAE PAGES TO:**

   → The study contact
   (see Investigator Site File for appropriate fax number).

   → If no photocopier <u>OR</u> fax is available, please telephone to the study contact.

5. **FOR ADDITIONAL INFORMATION, PLEASE CHECK THE "ADDITIONAL INFO" BOX AND FOLLOW THE PROCEDURE EXPLAINED AT POINT 4.**

Protocol	Center	Country	GSK Receipt Date	Subject Number
444563/006	|__|__|__|		|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

SERIOUS ADVERSE EVENT (SAE)

☐ **(1)** Initial report ☐ **(3)** Additional info
☐ **(2)** Additional info ☐ **(4)** Additional info

Subject Demography (1)

Initials: \|__\|__\| First name \|__\|__\| Family name

Date of birth: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

Gender : ☐ Male ☐ Female

Adverse Event *(please print clearly)* (2)

Diagnosis (or signs and symptoms if not known)

_____

_____

_____

For GSK

Date and time started : (3)
(Adverse event first symptoms) \|__\|__\| day \|__\|__\|__\|__\| month \|__\|__\|__\|__\| year \|__\|__\|:\|__\|__\| hours min

Date and time stopped : (4)
(If ongoing please leave blank) \|__\|__\| day \|__\|__\|__\|__\| month \|__\|__\|__\|__\| year \|__\|__\|:\|__\|__\| hours min

Intensity : (5)
(maximum)
☐ 1
☐ 2
☐ 3

In your opinion, did the vaccine possibly contribute to the SAE : (6)
☐ No
☐ Yes

Outcome : (7)
(maximum)
☐ 1 Recovered
☐ 2 Recovered with sequelae
☐ 3 Ongoing
☐ 4 Died

Action taken with respect to Study Vaccine (8)
☐ None
☐ Vaccination course postponed
☐ Vaccination course stopped

Events after further vaccination (9)
☐ Event reappeared
☐ Event did not reappear
☐ Unknown at this time
☐ Not applicable

♦ **Specify criteria for considering this as a Serious Adverse Event.** (10)
(mark all that apply).

1 ☐ Result in death
→ Autopsy ? ☐ No ☐ Yes
↓
Send autopsy report when available

2 ☐ Life threatening

3 ☐ Result in persistent or significant disability/incapacity

4 ☐ Requires in-patient hospitalization.
Admission date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

5 ☐ Prolongation of existing hospitalization
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year r

6 ☐ Congenital anomaly / birth defect in the offspring of a study subject.

7 ☐ "Medically important" event- specify:
_____

♦ **Other events (not SAE) to be reported in the same way:**
☐ Cancer

Other possible contributors: (11)
(mark all that apply)
☐ Medical history *(record in section 15)*
☐ Other medication *(record in section 14)*
☐ Protocol required procedure
☐ Other procedure
☐ Lack of efficacy
☐ Erroneous administration
☐ Other, specify : _____

(record additional information in section 19)

Was subject withdrawn due to this specific SAE ? (12)
☐ No
☐ Yes

Protocol				Subject Number
444563/006			**SAE (continued)**	|__|__|__|__|__|

Study vaccine Information **(13)**

Vaccine *(specify mixed or separate)*	Dose No	Lot No	Route / Site	Date
				|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|

Concomitant medication / vaccination that could have contributed to this SAE **(14)**

Drug / vaccine	Dosage	Frequency	Route	Start date	End date
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|

Relevant intercurrent illness & medical history that could have contributed to this SAE **(15)**
(Including allergies)

Condition :	Still present? : No ☐ Yes ☐
Condition :	Still present? : No ☐ Yes ☐

Drug(s) used to treat this SAE **(16)**

Drug	Dosage	Frequency	Route	Start date	End date
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|

Surgical treatment for this SAE *(please specify)* **(17)**

Description *(provide a brief narrative description of the SAE including relevant diagnostic findings, lab data & evolution of the events etc…)* **(18)**

Investigator signature Date :	(1) |__||__|__||__|__|__|__| day month year	(2) |__||__|__||__|__|__|__| day month year	(3) |__||__|__||__|__|__|__| day month year	(4) |__||__|__||__|__|__|__| day month year
Please PRINT name:				

	Signature	*Please PRINT name*	*Date*
CDM:			|__||__|__||__|__|__|__| day month year

AEGIS Number : |__|__|__|__|__|__|__|__|__|__| - |__|__|

Protocol				Subject Number
444563/006			**SAE (continued)**	|__|__|__|__|__|

Comments *(please provide further comments concerning the case)* **(19)**

Investigator signature Date :	(1) |__|__| |__|__|__|__| day month year	(2) |__|__| |__|__|__|__| day month year	(3) |__|__| |__|__|__|__| day month year	(4) |__|__| |__|__|__|__| day month year
Please PRINT name:				

	Signature	*Please PRINT name*	*Date*
CDM:			|__|__| |__|__|__|__| day month year

AEGIS Number : |__|__|__|__|__|__|__|__|__|__| - |__|__|

STUDY CONCLUSION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STUDY CONCLUSION

Has the code been broken?

☐ No
☐ Yes

Did any elimination criteria become applicable during the study?

☐ No
☐ Yes, please specify: _____

Has the subject dropped out of the study?
(a drop out is a subject who did not come back for the concluding visit foreseen in the protocol.)

☐ No
☐ Yes, please mark the **ONE most appropriate** category for drop out.

- ☐ (SAE) Serious adverse event (complete the **Serious Adverse Event form**).
- ☐ (AEX) Non-Serious adverse event (complete the **Non-serious Adverse Event form**).

  Please specify AE N°: _____
- ☐ (PTV) Protocol violation, please specify : _____
- ☐ (CWS) Consent withdrawal, not due to an adverse event.
- ☐ (MIG) Migrated / moved from the study area
- ☐ (LFU) Lost to follow-up.
- ☐ (OTH) Other, please specify : _____

Date of last contact : |__|__| |__|__|__| |__|__|__|__|
day month year

Was the subject in good condition at date of last contact ?

☐ No, please give details within the **Adverse Events section.**
☐ Yes

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this case report form, the Non-Serious Adverse Events and Serious Adverse Event sections including any laboratory data (if appropriate) and that all information is complete and accurate.

Date of last contact : |__|__| |__|__|__| |__|__|__|__|
day month year

Investigator signature :

Center	Subject identification	Subject Number
|__|__|__|	|__|__| First name |__|__| Family name	|__|__|__|__|__|

CONFIDENTIAL

WORKBOOK

444563/006 (Rota-006)
Amendment 3
Group HRV 2 doses

GlaxoSmithKline Biologicals

Rue de l'institut 89, B – 1330 Rixensart, Belgium
Tel: [redacted] Fax: [redacted]

Version 11.4
Date : May 14, 2002

GENERAL INSTRUCTIONS

Print clearly in **CAPITAL LETTERS** using a **black** fountain or ball-point pen and press firmly so that all copies are legible. Insert the writing board beneath all copies of the form being completed. Fill in the subject number on every page and answer all questions except where otherwise indicated.

Do not write in shaded areas which are qualified **"For GSK"**. Information written in these areas **are not the responsibility of the investigator**.
For each subject's **INITIALS**, please enter the first two letters of the first name and the first two letters of the family name.

ABBREVIATIONS: Abbreviations for medical conditions, clinical events or drug names should not be used. Units and route of administration of medication may be abbreviated. NA: not applicable.

IMPORTANT: Errors should be crossed out with a single line and the alteration made as near to the original as possible.
All alterations must be printed, initialed and dated by the investigator or authorized staff.

DATE

Use the following three-letter abbreviations for each month:

January	=	JAN
February	=	FEB
March	=	MAR
April	=	APR
May	=	MAY
June	=	JUN
July	=	JUL
August	=	AUG
September	=	SEP
October	=	OCT
November	=	NOV
December	=	DEC

Example : |0|1| |J|A|N| |2|0|0|2| = 1st January 2002
day month year

TIME

Unless specified otherwise, use the 24 hour clock :

Example: |1|5| : |3|0| = 3.30 p.m.
hours min

The **Medication** section, the **Concomitant Vaccination** section, the **Non-Serious Adverse Events** section and the **Serious Adverse Event (SAE)** form must be checked for final assessment at the end of the study.

For all subjects enrolled, please complete the **Conclusion after the first rotavirus season and the Study conclusion** forms.

ADVERSE EVENT DEFINITIONS

INTENSITY FOR SOLICITED SYMPTOMS

Cough/runny nose

0 : Normal
1 : Cough/runny nose which is easily tolerated
2 : Cough/runny nose which interferes with daily activity
3 : Cough/runny nose which prevents daily activity

Irritability/Fussiness

0 : Behavior as usual
1 : Crying more than usual / no effect on normal activity
2 : Crying more than usual / interferes with normal activity
3 : Crying that cannot be comforted / prevents normal activity

Loss of appetite

0 : Normal
1 : Eating less than usual / no effect on normal activity
2 : Eating less than usual / interferes with normal activity
3 : Not eating at all

GASTROENTERITIS EPISODES

Any diarrhea defined as three or more looser than normal stools within a day.

INTENSITY FOR NON-SOLICITED SYMPTOMS

0 : No adverse event.
1 : An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 : An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3 : An adverse event which prevents normal, everyday activities
(In a young child, such an adverse event would, for example, prevent attendance at school/kindergarten/ a day-care center and would cause the parents/guardians to seek medical advice).

ADVERSE EVENT DEFINITIONS

CAUSALITY

In your opinion, did the vaccine(s) possibly contribute to the adverse event?

NO : The adverse event is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the adverse event.

YES: There is a reasonable possibility that the vaccine contributed to the adverse event.

OUTCOME

1 : Recovered
2 : Recovered with sequelae
3 : Ongoing at study conclusion active phase or safety follow-up (whichever is applicable)
4 : Died
5 : Unknown

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that:

1 : results in death
2 : is life threatening
3 : results in persistent or significant disability / incapacity
4 : requires in-patient hospitalization
5 : prolongation of existing hospitalization
6 : is a congenital anomaly / birth defect in the offspring of a study subject
7 : In addition, important medical events (i.e. intussusception) that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not results in hospitalization; or development of drug dependency or drug abuse).

For each serious adverse event, please fill in the **Serious Adverse Event (SAE)** form and contact GlaxoSmithKline within 24 hours (one calendar day).

Although not considered as ‘serious adverse events’, cancers must be reported in the same way as serious adverse events.

GlaxoSmithKline Biologicals

444563/006 (Rota-006) – Amendment 3 – Group HRV 2 doses

FLOW SHEET

Age	**2 months**	**4 months**	**6 months**	**1 year**
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**FINAL VISIT**
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 *MO 4***	**Post vacc 2 MO *10***
Informed consent	•			
Medical history	•			
Check of inclusion criteria	•			
Check of exclusion criteria	•			
Check of elimination criteria		•	•	•
Check of contraindications	•	•	•	
Physical examination	•	•	•	•
Pre-vaccination body temperature	•	•	•	
Measure/record height and weight	•	•	•	•
Blood sampling	• (1 ml of blood)	• (1 ml of blood in a subset#)	• (3 mls of blood in a subset#)	• (3 mls of blood in a subset#, 1 ml ***for all other subjects receiving two doses***)
Randomisation	•			
Stool samples will be collected from a subset (N = 400) on the day of administration of dose 1 and dose 2 and on day 7 following each dose. ***Stool samples will be collected from a subset (N ~ 200) on the day of administration of dose 3 and on day 7 following dose 3***	•	•		
Study Vaccine	•	•		
Routine Vaccination	•	•	•	
Daily post-vaccination recording of solicited symptoms (days 0–14) by parents/guardians	•	•		
Collection of stool samples	•	•	•	•
Recording of solicited symptoms, non serious adverse events within 42 days after dose 1, dose 2 ***and dose 3 (in a subset)***, by investigator		•	•	
Contact (field visit) every week	◊	◊	◊	◊
Return of GE diary	•	•	•	•
GE diary transcription		•	•	•
Documentation of routine EPI vaccines	•	•	•	•
Recording medication	•	•	•	
Reporting of Serious Adverse Events occurring throughout the study period	•	•	•	•
Study Conclusion				•

#Subset for immunogenicity evaluation (N = 800)

◊ is used to indicate a study procedure which does not require documentation in the individual eCRFs.

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed. These intervals determine a subject's evaluability in the according to protocol analyses.

Intervals between study visits* ***for subjects receiving 2 doses of study vaccine/placebo will be as follows*** **(amended: 3-MAY-2002)**

Interval	Size of interval
1 (Visit 1→Visit 2)	49 - 83 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→ ***Final visit***)	160 - 200 days

*The date of the previous visit is the reference date.

VISIT 1

6 to 12 weeks of age

DOSE 1

Informed Consent has to be obtained prior to any study procedure

ELIGIBILITY CHECKLIST

INCLUSION CRITERIA

All subjects enrolled must satisfy the following criteria at study entry :

1. A male or female child between, and including 6 and 12 weeks (42-90 days) of age at the time of the first vaccination.
2. Free of obvious health problems as established by medical history and clinical examination before entering into the study.
3. Written informed consent obtained from the parents or guardians of the subject.
4. Born after a gestation period (between 36 and 42 weeks) or a birth weight > 2000g.

EXCLUSION CRITERIA FOR ENROLMENT

The following criteria should be checked at the time of study entry. If any apply at the time of study entry, the subject must not be included in the study :

5. Use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the study vaccine or placebo or planned use during the study period.
6. Planned administration of a vaccine (including routine pediatric vaccines) not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.
7. Planned administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
8. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth. (Topical steroids are allowed.)
9. History of diphtheria, tetanus, pertussis, Hib disease and/ or hepatitis B.
10. Previous vaccination against diphtheria, tetanus, pertussis, and/or Haemophilus influenzae type b.
11. Use of antibiotics within 7 days preceding dose 1 (Warrants deferral of vaccination pending recovery of the subject).
12. Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the GI tract or other serious medical condition as determined by the investigator.
13. Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
14. History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.
15. Acute disease at time of enrollment. (Acute disease is defined as the presence of moderate or severe illness with or without fever i.e. temperature ≥ 37.5°C as measured by an axillary thermometer or ≥ 38.0°C as measured by a rectal thermometer). A temperature greater than or equal to these cut-off warrants deferral of the vaccination pending recovery of the subject. (amended: 12-FEB-2001)
16. Gastroenteritis within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).
17. Household contact with an immunosuppressed individual or pregnant women.
18. Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
19. Previous confirmed occurrence of rotavirus gastroenteritis.

ELIMINATION CRITERIA DURING THE STUDY UP TO VISIT 3

The following criteria should be checked at visits 2 and 3. If any become applicable during the study, the subject will not be required to discontinue the study but may be eliminated from the according-to-protocol analysis.

1. Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
2. Use of antibiotics during the period starting from 7 days before dose 1 and 2 and ending 7 days after.
3. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
4. Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of vaccine(s) and ending 14 days after.
5. Administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
6. Administration of immunoglobulins and/or any blood products during the study period.
7. Confirmed immunosuppressive or immunodeficient condition, including HIV.

ELIMINATION CRITERIA DURING THE STUDY FROM VISIT 3 UNTIL THE FINAL STUDY VISIT

The following criteria should be checked at the final study visit for all subjects. If any become applicable during the study, the subject may be eliminated from the according-to-protocol analysis.

8. Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
9. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
10. Administration of immunoglobulins and/or any blood products during the study period.
11. Confirmed immunosuppressive or immunodeficient condition, including HIV.

Contraindications to vaccination

SB Biologicals' HRV vaccine or placebo:

The following adverse events constitute absolute contraindications to further administration of human rotavirus vaccine or placebo; if any of these adverse events occur during the study, the subject must not receive additional doses of vaccine or placebo but may continue other study procedures at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event :

- Hypersensitivity reaction due to the vaccine.
- Intussusception.

The following adverse events constitute contraindications to administration of human rotavirus vaccine or placebo at a given point in time; if any one of these adverse events occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol or withdrawn at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event.

- Axillary/rectal temperature ≥37.5°C/38.0°C
- Gastroenteritis within 7 days preceding the study vaccine administration.

DTPw-HB+Hib vaccine:

The following adverse events constitute absolute contraindications or precautions to further administration of DTPw-HB+Hib vaccine; if any of these adverse events occurs during the study, the subject must be withdrawn and must be followed until resolution of the event, as with any adverse event :

Absolute contraindications:

- Known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B or Hib vaccines.
- Encephalopathy (not due to another identifiable cause). This is defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, and/or generalized or focal seizures that persist more than a few hours, with failure to recover within 24 hours. Even though causation by DTP-containing vaccine cannot be established, no subsequent doses of pertussis vaccine should be given.

Precautions:

- *If the following adverse events occur in temporal relation to DTPw-HB+Hib vaccine administration, the decision to administer additional doses of DTPw-HB+Hib vaccine should be carefully considered:*
- Fever ≥ 40.5°C/≥ 40.0°C (rectal/axillary temperature) within 48 hours of vaccination not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting >3 hours, occurring within 48 hours of vaccination.
- Seizures with or without fever occurring within 3 days of vaccination.

Protocol	Center	Visit	Date of visit	Subject Number
444563/006	|__|__|__|	**VISIT 1**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date : |__|__| |__|__|__| |__|__|__|__|
day month year

DEMOGRAPHICS

Subject initials : |__|__| |__|__|
First name Family name

Date of birth : |__|__| |__|__|__| |__|__|__|__|
day month year

Gender :
- ☐ Male
- ☐ Female

Race :
- ☐ (WH) White
- ☐ (BL) Black
- ☐ (OR) Oriental
- ☐ (OT) Other, please specify: _____

Height : |__|__|__| cm

Weight : |__|__|__| . |__| kg

Is the subject eligible for the study, according to the criteria listed hereby ?

- ☐ Yes
- ☐ No, please give the corresponding criterion number(s) : _____

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

GENERAL MEDICAL HISTORY / PHYSICAL EXAMINATION

Are you aware of any pre-existing conditions or signs and/or symptoms present in the subject prior to the start of the study ?

☐ No

☐ Yes, please check appropriate box(es) and give diagnosis

			PAST	CURRENT		DIAGNOSIS
____	10	Cutaneous	☐	☐	1	----------
			☐	☐	2	----------
____	5	Eyes	☐	☐	1	----------
			☐	☐	2	----------
____	6	Ears-nose-throat	☐	☐	1	----------
			☐	☐	2	----------
____	2	Cardiovascular	☐	☐	1	----------
			☐	☐	2	----------
____	3	Respiratory	☐	☐	1	----------
			☐	☐	2	----------
____	1	Gastrointestinal	☐	☐	1	----------
			☐	☐	2	----------
____	7	Musculoskeletal	☐	☐	1	----------
			☐	☐	2	----------
____	8	Neurological	☐	☐	1	----------
			☐	☐	2	----------
____	12	Genitourinary	☐	☐	1	----------
			☐	☐	2	----------
____	11	Haematology	☐	☐	1	----------
			☐	☐	2	----------
____	4	Allergies	☐	☐	1	----------
			☐	☐	2	----------
____	9	Endocrine	☐	☐	1	----------
			☐	☐	2	----------
____	99	Other (specify)	☐	☐	1	----------
			☐	☐	2	----------

Please report medication(s) as specified in the protocol and fill in the **Medication** section.

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary ☐ Rectal

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes ☐ No

STOOL SAMPLE (only for a subset)

Has a stool sample been taken at the day of or 1 day prior to vaccination ?

☐ Yes
☐ No ☐ NA

Has a stool sample been taken at day 7 ± 1 ?

☐ Yes
☐ No ☐ NA

→ *** please fill the stools collection section if any stools have been collected.**

FEEDINGS

Is the child fed with : ☐ breast milk
☐ infant formula
☐ both

Did the child :
☐ receive no food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination but not 30 minutes after vaccination ?
☐ receive food within 30 minutes after vaccination but not 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / Site Route**	**Has the study vaccine been administered according to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please specify (*)*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes ☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	☐ No ☐ Yes→	___ ___ ____	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	__	__	__	__	__	__	__	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	___ ___ ____	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	__	__	__	__	__	__	__	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	___ ___ ____	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	__	__	__	__	__	__	__	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	___ ___ ____	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	__	__	__	__	__	__	__	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	___ ___ ____	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	__	__	__	__	__	__	__	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	Please fill the **GE Episodes** Section	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0 1 2 3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 2

4 months of age

(49 – 83 days after Visit 1)

DOSE 2

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION / VACCINATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the **Contraindications** as specified in the protocol.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected.

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 2**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 1 until visit 2 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary
☐ Rectal

LABORATORY TESTS (only for a subset)

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes
☐ No ☐ NA

STOOL SAMPLE (only for a subset)

Has a stool sample been taken at the day of or 1 day prior to vaccination ?

☐ Yes
☐ No ☐ NA

Has a stool sample been taken at day 7 ± 1 ?

☐ Yes
☐ No ☐ NA

→ *** please fill the stools collection section if any stools have been collected.**

FEEDINGS

Is the child fed with :
☐ breast milk
☐ infant formula
☐ both

Did the child :
☐ receive no food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination but not 30 minutes after vaccination ?
☐ receive food within 30 minutes after vaccination but not 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 2**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / Site Route**	**Has the study vaccine been administered according to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please specify (*)*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes ☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__._ ☐ not taken	__._ ☐ not taken	__._ ☐ not taken	__._ ☐ not taken	__._ ☐ not taken	__._ ☐ not taken	__._ ☐ not taken	__._ ☐ not taken	__._ ☐ not taken	__._ ☐ not taken	__._ ☐ not taken	__._ ☐ not taken	__._ ☐ not taken	__._ ☐ not taken	__._ ☐ not taken	☐ No ☐ Yes→	___ ___ ____	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	__	__	__	__	__	__	__	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	___ ___ ____	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	__	__	__	__	__	__	__	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	___ ___ ____	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	__	__	__	__	__	__	__	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	___ ___ ____	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	__	__	__	__	__	__	__	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	___ ___ ____	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	__	__	__	__	__	__	__	__	__	__	__	__	__	__	__	☐ No ☐ Yes→	Please fill the **GE Episodes** Section	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0 1 2 3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 3

6 months of age

(49 – 83 days after Visit 2)

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION / VACCINATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the **Contraindications** as specified in the protocol.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected.

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 3**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 2 until visit 3 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary
☐ Rectal

LABORATORY TESTS (only for a subset)

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes
☐ No ☐ NA

Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

FINAL VISIT

1 YEAR OF AGE

(160 – 200 days after Visit 3)

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

CONCOMITANT VACCINATION

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected.

Protocol		Visit	Date of visit	Subject Number
444563/006		**FINAL VISIT**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from visit 3 until visit 4 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ?

☐ Yes
☐ No

STOOLS COLLECTION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STOOLS COLLECTION

STOOLS 1	STOOLS 2	STOOLS 3
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 4	**STOOLS 5**	**STOOLS 6**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 7	**STOOLS 8**	**STOOLS 9**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 10	**STOOLS 11**	**STOOLS 12**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 13	**STOOLS 14**	**STOOLS 15**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 16	**STOOLS 17**	**STOOLS 18**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STOOLS COLLECTION (continued)

STOOLS 19	STOOLS 20	STOOLS 21
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 22	**STOOLS 23**	**STOOLS 24**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 25	**STOOLS 26**	**STOOLS 27**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 28	**STOOLS 29**	**STOOLS 30**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 31	**STOOLS 32**	**STOOLS 33**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 34	**STOOLS 35**	**STOOLS 36**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min

GASTROENTERITIS EPISODES

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

CONCOMITANT VACCINATION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administered during the timeframe as specified in the protocol ?

☐ No

☐ Yes, please record concomitant vaccination with trade name and / or generic name, and vaccine administration date.

Trade / Generic Name	**Administration date** day month year
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	

MEDICATION

GlaxoSmithKline Biologicals

MEDICATION ROUTE

CODE	LABEL
EXT	External
ID	Intradermal
IH	Inhalation
IM	Intramuscular
IR	Intraarticular
IT	Intrathecal
IV	Intravenous
NA	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

Protocol				Subject Number
444563/006				|__|__|__|__|__|

MEDICATION

→Any immunosuppressants or other immune-modifying drugs or treatments administered at ANY time during the period starting 30 days prior to the first dose of study vaccine and ending at Visit 3 must be recorded with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment. Any antibiotics administered within 7 days preceding each study vaccine/placebo administration and during the first 7 days after each study vaccine/placebo administration and any antipyretics administered at ANY time during the period starting 30 days prior to the first dose of study vaccine and ending one month (minimum 30 days) after the last dose of study vaccine/placebo must be recorded with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment.

→Any other concomitant medication administered prophylactically in anticipation of reaction to the vaccination must also be recorded with trade name and/or generic name of the medication, total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'

Have any of the above mentioned medications/treatments been administered during study period?

☐ No
☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or check box if continuing at end of study day month year	
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					

NON-SERIOUS ADVERSE EVENTS

Protocol				Subject Number
444563/006				|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS

(Please report all **serious adverse events** only on the **Serious Adverse Event (SAE)** form).

Have any **non-serious adverse events** occurred within **42 days** post-vaccination, excluding those recorded on the **Solicited Adverse Events** pages ?

☐ No
☐ Yes, please complete the following table.

AE No.	**AE.1**	**AE.2**	**AE.3**
Description	----------	----------	----------
	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)
For GSK			
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3
Causality In your opinion, did the vaccine possibly contribute to this AE ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Outcome	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown

Protocol				Subject Number
444563/006				|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS (continued)

.

AE No.	**AE.4**	**AE.5**	**AE.6**
Description	----------	----------	----------
	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)
For GSK			
Date Started	|__|__||__|__|__||__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__||__|__|__||__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__||__|__|__||__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol
Date Stopped	|__|__||__|__|__||__|__|__|__| day month year	|__|__||__|__|__||__|__|__|__| day month year	|__|__||__|__|__||__|__|__|__| day month year
Intensity	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3
Causality In your opinion, did the vaccine possibly contribute to this AE ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Outcome	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown

SERIOUS ADVERSE EVENT

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EVENT (SAE)

SAE's MUST BE REPORTED TO GLAXOSMITHKLINE BIOLOGICALS WITHIN 24 HOURS

1. **COMPLETE THE SAE PAGES OPPOSITE.**
   Please complete these pages as fully and accurately as possible in order to minimize the time you spend dealing with data queries.

   If the SAE is still ongoing at the time of reporting, please leave "Outcome" blank and update it later.

2. **PLEASE ENSURE THAT ALL INFORMATION ON THE SAE PAGES IS CONSISTENT WITH THE FOLLOWING OTHER CRF PAGES.**
   - Demographics
   - General Medical History / Physical Examination
   - Vaccine Administration page(s) (for doses administered)
   - Medication
   - Concomitant Vaccination

3. **SIGN AND DATE THE SAE PAGES 2 (AND 3). COMPLETE PAGE 3 OF THE SAE FORM IF NEEDED <u>ONLY</u>.**

4. **PHOTOCOPY THE SAE PAGES (DO NOT SEPARATE THE NCR PAGES) AND FAX THE COPY OF THE SAE PAGES TO:**
   → The study contact
   (see Investigator Site File for appropriate fax number).

   → If no photocopier <u>OR</u> fax is available, please telephone the study contact.

5. **FOR ADDITIONAL INFORMATION, PLEASE CHECK THE "ADDITIONAL INFO" BOX AND FOLLOW THE PROCEDURE EXPLAINED AT POINT 4.**

Protocol	Center	Country	GSK Receipt Date	Subject Number
444563/006	|__|__|__|		|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

SERIOUS ADVERSE EVENT (SAE)

☐ **(1)** Initial report ☐ **(3)** Additional info
☐ **(2)** Additional info ☐ **(4)** Additional info

Subject Demography (1)

Initials: \|__\|__\| First name \|__\|__\| Family name

Date of birth: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

Gender : ☐ Male ☐ Female

Adverse Event *(please print clearly)* (2)

Diagnosis (or signs and symptoms if not known)

_____

_____

_____

For GSK

Date and time started : (3)
(Adverse event first symptoms) \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\| day month year hours min

Date and time stopped : (4)
(If ongoing please leave blank) \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\| day month year hours min

Intensity : (5)
(maximum)
☐ 1
☐ 2
☐ 3

In your opinion, did the vaccine possibly contribute to the SAE : (6)
☐ No
☐ Yes

Outcome : (7)
(maximum)
☐ 1 Recovered
☐ 2 Recovered with sequelae
☐ 3 Ongoing
☐ 4 Died

Action taken with respect to Study Vaccine (8)
☐ None
☐ Vaccination course postponed
☐ Vaccination course stopped

Events after further vaccination (9)
☐ Event reappeared
☐ Event did not reappear
☐ Unknown at this time
☐ Not applicable

♦ **Specify criteria for considering this as a Serious Adverse Event.** (10)
(mark all that apply).

1. ☐ Result in death
   → Autopsy ? ☐ No ☐ Yes
   ↓
   Send autopsy report when available
2. ☐ Life threatening
3. ☐ Result in persistent or significant disability/incapacity
4. ☐ Requires in-patient hospitalization.
   Admission date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year
   Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year
5. ☐ Prolongation of existing hospitalization
   Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year
6. ☐ Congenital anomaly / birth defect in the offspring of a study subject.
7. ☐ "Medically important" event- specify: _____

♦ **Other events (not SAE) to be reported in the same way:**
☐ Cancer

Other possible contributors: (11)
(mark all that apply)
☐ Medical history *(record in section 15)*
☐ Other medication *(record in section 14)*
☐ Protocol required procedure
☐ Other procedure
☐ Lack of efficacy
☐ Erroneous administration
☐ Other, specify : _____

(record additional information in section 19)

Was subject withdrawn due to this specific SAE ? (12)
☐ No
☐ Yes

Protocol				Subject Number
444563/006			**SAE (continued)**	|__|__|__|__|__|

Study vaccine Information **(13)**

Vaccine *(specify mixed or separate)*	Dose No	Lot No	Route / Site	Date
				|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|

Concomitant medication / vaccination that could have contributed to this SAE **(14)**

Drug / vaccine	Dosage	Frequency	Route	Start date	End date
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|

Relevant intercurrent illness & medical history that could have contributed to this SAE **(15)**
(Including allergies)

Condition :	Still present? : No ☐ Yes ☐
Condition :	Still present? : No ☐ Yes ☐

Drug(s) used to treat this SAE **(16)**

Drug	Dosage	Frequency	Route	Start date	End date
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|
				|__||__|__||__|__|__|__|	|__||__|__||__|__|__|__|

Surgical treatment for this SAE *(please specify)* **(17)**

Description *(provide a brief narrative description of the SAE including relevant diagnostic findings, lab data & evolution of the events etc…)* **(18)**

Investigator signature Date :	(1) |__||__|__||__|__|__|__| day month year	(2) |__||__|__||__|__|__|__| day month year	(3) |__||__|__||__|__|__|__| day month year	(4) |__||__|__||__|__|__|__| day month year
Please PRINT name:				

For GSK Rixensart	*Signature*	*Please PRINT name*	*Date*
Clinical Development Manager:			|__||__|__||__|__|__|__| day month year

AEGIS Number : |__|__|__|__|__|__|__|__|__|__| • |__|__|

Protocol				Subject Number
444563/006			**SAE (continued)**	|__|__|__|__|__|

Comments *(provide further comments concerning the case)* **(19)**

Investigator signature Date :	(1) |__|__| |__|__|__| |__|__|__|__| day month year	(2) |__|__| |__|__|__| |__|__|__|__| day month year	(3) |__|__| |__|__|__| |__|__|__|__| day month year	(4) |__|__| |__|__|__| |__|__|__|__| day month year
Please PRINT name:				

For GSK Rixensart	*Signature*	*Please PRINT name*	*Date*
Clinical Development Manager:			|__|__| |__|__|__| |__|__|__|__| day month year

AEGIS Number : |__|__|__|__|__|__|__|__|__|__| · |__|__|

STUDY CONCLUSION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STUDY CONCLUSION

Has the code been broken?

☐ No
☐ Yes

Did any elimination criteria become applicable during the study?

☐ No
☐ Yes, please specify: _____

Has the subject dropped out of the study?
(a drop out is a subject who did not come back for the concluding visit foreseen in the protocol.)

☐ No
☐ Yes, please mark the **ONE most appropriate** category for drop out.

- ☐ (SAE) Serious adverse event (complete the **Serious Adverse Event form**).
- ☐ (AEX) Non-Serious adverse event (complete the **Non-serious Adverse Event form**).

  please specify AE N°: _____
- ☐ (PTV) Protocol violation, please specify : _____
- ☐ (CWS) Consent withdrawal, not due to an adverse event.
- ☐ (MIG) Migrated / moved from the study area
- ☐ (LFU) Lost to follow-up.
- ☐ (OTH) Other, please specify : _____

Date of last contact : |__|__| |__|__|__| |__|__|__|__|
day month year

Was the subject in good condition at date of last contact?

☐ No, please give details within the **Adverse Events section.**
☐ Yes

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this case report form, the Non-Serious Adverse Events and Serious Adverse Event sections including any laboratory data (if appropriate) and that all information is complete and accurate.

Date : |__|__| |__|__|__| |__|__|__|__|
day month year

Investigator signature :

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	**SOLICITED SYMPTOMS**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose
- **0**: Normal
- **1**: Cough/runny nose which is easily tolerated
- **2**: Cough/runny nose which interferes with daily activity
- **3**: Cough/runny nose which prevents daily activity

Irritability / fussiness:
- **0**: Behavior as usual
- **1**: Crying more than usual / no effect on normal activity
- **2**: Crying more than usual / interferes with normal activity
- **3**: Crying that cannot be comforted/ prevents normal activity

Loss of appetite:
- 0: Normal
- 1: Eating less than usual / no effect on normal activity
- 2: Eating less than usual / interferes with normal activity
- 3: Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given.

SOLICITED SYMPTOMS	Day 0	Day 1 evening	Day 2 evening	Day 3 evening	Day 4 evening	Day 5 evening	Day 6 evening	Day 7 evening	Day 8 evening	Day 9 evening	Day 10 evening	Day 11 evening	Day 12 evening	Day 13 evening	Day 14 evening	Ongoing after day 14?	Date of last day of symptoms day month year
Date:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____		
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Irritability/fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	**if ongoing after day 14, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET**
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

MEDICATION FOR DIARRHEA
- ☐ None
- ☐ Oral rehydration
- ☐ Other, please specify----------

HOSPITALISATION FOR DIARRHEA :
- ☐ No
- ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__||__|__|__||__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 14**	**DOSE 1**	|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea.

SOLICITED GASTROENTERITIS SYMPTOMS	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__| |__|__|__| |__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	GASTROENTERITIS EPISODES		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS is defined as presence of diarrhea
DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	**OTHER GENERAL SYMPTOMS AND MEDICATION**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

INTENSITY:

Other general symptoms:

1: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse event which prevents normal, everyday activities. (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten / a day-care center and would cause the parents / guardians to seek medical advice).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis symptoms) Please give details below	Intensity	Start date day month year	End date or check box if continuing day month year	
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

MEDICATION Please fill in below if any medication has been taken since the vaccination **(excluding oral rehydration)**		Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
Trade / generic name	Reason				
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**SOLICITED SYMPTOMS**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose
- **0**: Normal
- **1**: Cough/runny nose which is easily tolerated
- **2**: Cough/runny nose which interferes with daily activity
- **3**: Cough/runny nose which prevents daily activity

Irritability / fussiness:
- **0**: Behavior as usual
- **1**: Crying more than usual / no effect on normal activity
- **2**: Crying more than usual / interferes with normal activity
- **3**: Crying that cannot be comforted/ prevents normal activity

Loss of appetite:
- 0: Normal
- 1: Eating less than usual / no effect on normal activity
- 2: Eating less than usual / interferes with normal activity
- 3: Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given.

SOLICITED SYMPTOMS	Day 0	Day 1 evening	Day 2 evening	Day 3 evening	Day 4 evening	Day 5 evening	Day 6 evening	Day 7 evening	Day 8 evening	Day 9 evening	Day 10 evening	Day 11 evening	Day 12 evening	Day 13 evening	Day 14 evening	Ongoing after day 14?	Date of last day of symptoms day month year
Date:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____		
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Irritability/fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	**if ongoing after day 14, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET**
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

MEDICATION FOR DIARRHEA
- ☐ None
- ☐ Oral rehydration
- ☐ Other, please specify----------

HOSPITALISATION FOR DIARRHEA :
- ☐ No
- ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__|/|__|__|__|/|__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 14**	**DOSE 2**	|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea.

SOLICITED GASTROENTERITIS SYMPTOMS	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__| |__|__|__| |__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**GASTROENTERITIS EPISODES**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS is defined as presence of diarrhea.
DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episode of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and/or vomiting and record whether medical treatment was given

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**OTHER GENERAL SYMPTOMS AND MEDICATION**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

INTENSITY:

Other general symptoms:

1: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse event which prevents normal, everyday activities. (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten / a day-care center and would cause the parents / guardians to seek medical advice).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis symptoms) Please give details below	Intensity	Start date day month year	End date or check box if continuing day month year	
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

MEDICATION Please fill in below if any medication has been taken since the vaccination **(excluding oral rehydration)**		Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
Trade / generic name	Reason				
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

Center	Subject identification	Subject Number
|__|__|__|	|__|__| First name |__|__| Family name	|__|__|__|__|__|

CONFIDENTIAL

WORKBOOK

444563/006 (Rota-006)
Amendment 3
Group HRV 3 doses

GlaxoSmithKline Biologicals

Rue de l'institut 89, B – 1330 Rixensart, Belgium
Tel: [redacted] Fax: [redacted]

Version 11.4
Date : May 17, 2002

GENERAL INSTRUCTIONS

Print clearly in **CAPITAL LETTERS** using a **black** fountain or ball-point pen and press firmly so that all copies are legible. Insert the writing board beneath all copies of the form being completed. Fill in the subject number on every page and answer all questions except where otherwise indicated.

Do not write in shaded areas which are qualified **"For GSK"**. Information written in these areas **are not the responsibility of the investigator**.
For each subject's **INITIALS**, please enter the first two letters of the first name and the first two letters of the family name.

ABBREVIATIONS: Abbreviations for medical conditions, clinical events or drug names should not be used. Units and route of administration of medication may be abbreviated. NA: not applicable.

IMPORTANT: Errors should be crossed out with a single line and the alteration made as near to the original as possible.
All alterations must be printed, initialed and dated by the investigator or authorized staff.

DATE

Use the following three-letter abbreviations for each month:

January	=	JAN
February	=	FEB
March	=	MAR
April	=	APR
May	=	MAY
June	=	JUN
July	=	JUL
August	=	AUG
September	=	SEP
October	=	OCT
November	=	NOV
December	=	DEC

Example : |0|1| |J|A|N| |2|0|0|2| = 1st January 2002
day month year

TIME

Unless specified otherwise, use the 24 hour clock :

Example: |1|5| : |3|0| = 3.30 p.m.
hours min

The **Medication** section, the **Concomitant Vaccination** section, the **Non-Serious Adverse Events** section and the **Serious Adverse Event (SAE)** form must be checked for final assessment at the end of the study.

For all subjects enrolled, please complete the **Conclusion after the first rotavirus season and the Study conclusion** forms.

ADVERSE EVENT DEFINITIONS

INTENSITY FOR SOLICITED SYMPTOMS

Cough/runny nose

0 : Normal
1 : Cough/runny nose which is easily tolerated
2 : Cough/runny nose which interferes with daily activity
3 : Cough/runny nose which prevents daily activity

Irritability/Fussiness

0 : Behavior as usual
1 : Crying more than usual / no effect on normal activity
2 : Crying more than usual / interferes with normal activity
3 : Crying that cannot be comforted / prevents normal activity

Loss of appetite

0 : Normal
1 : Eating less than usual / no effect on normal activity
2 : Eating less than usual / interferes with normal activity
3 : Not eating at all

GASTROENTERITIS EPISODES

Any diarrhea defined as three or more looser than normal stools within a day.

INTENSITY FOR NON-SOLICITED SYMPTOMS

0 : No adverse event.
1 : An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 : An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3 : An adverse event which prevents normal, everyday activities
(In a young child, such an adverse event would, for example, prevent attendance at school/kindergarten/ a day-care center and would cause the parents/guardians to seek medical advice).

ADVERSE EVENT DEFINITIONS

CAUSALITY

In your opinion, did the vaccine(s) possibly contribute to the adverse event?

NO : The adverse event is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the adverse event.

YES: There is a reasonable possibility that the vaccine contributed to the adverse event.

OUTCOME

1 : Recovered
2 : Recovered with sequelae
3 : Ongoing at study conclusion active phase or safety follow-up (whichever is applicable)
4 : Died
5 : Unknown

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that:

1 : results in death
2 : is life threatening
3 : results in persistent or significant disability / incapacity
4 : requires in-patient hospitalization
5 : prolongation of existing hospitalization
6 : is a congenital anomaly / birth defect in the offspring of a study subject
7 : In addition, important medical events (i.e. intussusception) that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not results in hospitalization; or development of drug dependency or drug abuse).

For each serious adverse event, please fill in the **Serious Adverse Event (SAE)** form and contact GlaxoSmithKline within 24 hours (one calendar day).

Although not considered as ‘serious adverse events’, cancers must be reported in the same way as serious adverse events.

GlaxoSmithKline Biologicals

444563/006 (Rota-006) – Amendment 3 – Group HRV 3 doses

FLOW SHEET

Age	**2 months**	**4 months**	**6 months**	***8 months***	**1 year**
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	***VISIT 4*** ***DOSE 3 SUBSET ONLY****	**FINAL VISIT**
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2** ***MO 4***	***Post vacc 3 MO 6***	**Post vacc 2 MO *10***
Informed consent	•				
Medical history	•				
Check of inclusion criteria	•				
Check of exclusion criteria	•				
Check of elimination criteria		•	•	•	•
Check of contraindications	•	•	•		
Physical examination	•	•	•	•	•
Pre-vaccination body temperature	•	•	•		
Measure/record height and weight	•	•	•	•	•
Blood sampling	• (1 ml of blood)	• (1 ml of blood in a subset#)	• (3 mls of blood in a subset#) • ***(1 ml of blood in dose 3 subset*)***	• ***(3 mls of blood in dose 3 subset*)***	• (3 mls of blood in a subset#, 1 ml ***for subjects receiving two doses***)
Randomisation	•				
Stool samples will be collected from a subset (N = 400) on the day of administration of dose 1 and dose 2 and on day 7 following each dose. ***Stool samples will be collected from a subset (N ~ 200) on the day of administration of dose 3 and on day 7 following dose 3***	•	•	•		
Study Vaccine	•	•	• ***(dose 3 subset*)***		
Routine Vaccination	•	•	•		
Daily post-vaccination recording of solicited symptoms (days 0–14) by parents/guardians	•	•	• ***(dose 3 subset*)***		
Collection of stool samples	•	•	•	• ***(dose 3 subset*)***	•
Recording of solicited symptoms, non serious adverse events within 42 days after dose 1, dose 2 ***and dose 3 (in a subset)***, by investigator		•	•	• ***(dose 3 subset*)***	
Contact (field visit) every week	◊	◊	◊	◊	◊
Return of GE diary	•	•	•	• ***(dose 3 subset*)***	•
GE diary transcription		•	•	• ***(dose 3 subset*)***	•
Documentation of routine EPI vaccines	•	•	•	• ***(dose 3 subset*)***	•
Recording medication	•	•	•	• ***(dose 3 subset*)***	
Reporting of Serious Adverse Events occurring throughout the study period	•	•	•	• ***(dose 3 subset*)***	•
Study Conclusion					•

#Subset for immunogenicity evaluation (N = 800)
****Subset receiving three doses of study vaccine/placebo (N = 200)***

◊ is used to indicate a study procedure which does not require documentation in the individual eCRFs.

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed. These intervals determine a subject's evaluability in the according to protocol analyses.

Intervals between study visits* for subjects included in the subset receiving 3 doses of study vaccine/placebo will be as follows **(amended: 3-MAY-2002)**

Interval	***Size of interval***
1 (Visit 1→Visit 2)	***49 - 83 days***
2 (Visit 2→Visit 3)	***49 - 83 days***
3 (Visit 3→Visit 4)	***49 – 83 days***
4 (Visit 3→Final visit)	***160 - 200 days***

*The date of the previous visit is the reference date.

VISIT 1

6 to 12 weeks of age

DOSE 1

Informed Consent has to be obtained prior to any study procedure

ELIGIBILITY CHECKLIST

INCLUSION CRITERIA

All subjects enrolled must satisfy the following criteria at study entry :

1. A male or female child between, and including 6 and 12 weeks (42-90 days) of age at the time of the first vaccination.
2. Free of obvious health problems as established by medical history and clinical examination before entering into the study.
3. Written informed consent obtained from the parents or guardians of the subject.
4. Born after a gestation period (between 36 and 42 weeks) or a birth weight > 2000g.

EXCLUSION CRITERIA FOR ENROLMENT

The following criteria should be checked at the time of study entry. If any apply at the time of study entry, the subject must not be included in the study :

5. Use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the study vaccine or placebo or planned use during the study period.
6. Planned administration of a vaccine (including routine pediatric vaccines) not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.
7. Planned administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
8. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth. (Topical steroids are allowed.)
9. History of diphtheria, tetanus, pertussis, Hib disease and/ or hepatitis B.
10. Previous vaccination against diphtheria, tetanus, pertussis, and/or Haemophilus influenzae type b.
11. Use of antibiotics within 7 days preceding dose 1 (Warrants deferral of vaccination pending recovery of the subject).
12. Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the GI tract or other serious medical condition as determined by the investigator.
13. Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
14. History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.
15. Acute disease at time of enrollment. (Acute disease is defined as the presence of moderate or severe illness with or without fever i.e. temperature ≥ 37.5°C as measured by an axillary thermometer or ≥ 38.0°C as measured by a rectal thermometer). A temperature greater than or equal to these cut-off warrants deferral of the vaccination pending recovery of the subject. (amended: 12-FEB-2001)
16. Gastroenteritis within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).
17. Household contact with an immunosuppressed individual or pregnant women.
18. Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
19. Previous confirmed occurrence of rotavirus gastroenteritis.

ELIMINATION CRITERIA DURING THE STUDY UP TO VISIT 4

The following criteria should be checked at visits 2 and 3. These elimination criteria should be also checked on the day of dose 3 of study vaccine/placebo in the subset of subjects who receive the third dose (at Visit 4) If any become applicable during the study, the subject will not be required to discontinue the study but may be eliminated from the according-to-protocol analysis.

1. Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
2. Use of antibiotics during the period starting from 7 days before dose 1 and 2 and ending 7 days after.
3. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
4. Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of vaccine(s) and ending 14 days after.
5. Administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
6. Administration of immunoglobulins and/or any blood products during the study period.
7. Confirmed immunosuppressive or immunodeficient condition, including HIV.

ELIMINATION CRITERIA DURING THE STUDY FROM VISIT 4 UNTIL THE FINAL STUDY VISIT

The following criteria should be checked at the final study visit for all subjects. If any become applicable during the study, the subject may be eliminated from the according-to-protocol analysis.

8. Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
9. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
10. Administration of immunoglobulins and/or any blood products during the study period.
11. Confirmed immunosuppressive or immunodeficient condition, including HIV.

Contraindications to vaccination

SB Biologicals' HRV vaccine or placebo:

The following adverse events constitute absolute contraindications to further administration of human rotavirus vaccine or placebo; if any of these adverse events occur during the study, the subject must not receive additional doses of vaccine or placebo but may continue other study procedures at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event :

- Hypersensitivity reaction due to the vaccine.
- Intussusception.

The following adverse events constitute contraindications to administration of human rotavirus vaccine or placebo at a given point in time; if any one of these adverse events occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol or withdrawn at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event.

- Axillary/rectal temperature ≥37.5°C/38.0°C
- Gastroenteritis within 7 days preceding the study vaccine administration.

DTPw-HB+Hib vaccine:

The following adverse events constitute absolute contraindications or precautions to further administration of DTPw-HB+Hib vaccine; if any of these adverse events occurs during the study, the subject must be withdrawn and must be followed until resolution of the event, as with any adverse event :

Absolute contraindications:

- Known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B or Hib vaccines.
- Encephalopathy (not due to another identifiable cause). This is defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, and/or generalized or focal seizures that persist more than a few hours, with failure to recover within 24 hours. Even though causation by DTP-containing vaccine cannot be established, no subsequent doses of pertussis vaccine should be given.

Precautions:

- *If the following adverse events occur in temporal relation to DTPw-HB+Hib vaccine administration, the decision to administer additional doses of DTPw-HB+Hib vaccine should be carefully considered:*
- Fever ≥ 40.5°C/≥ 40.0°C (rectal/axillary temperature) within 48 hours of vaccination not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting >3 hours, occurring within 48 hours of vaccination.
- Seizures with or without fever occurring within 3 days of vaccination.

Protocol	Center	Visit	Date of visit	Subject Number
444563/006	|__|__|__|	**VISIT 1**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date : |__|__| |__|__|__| |__|__|__|__|
day month year

DEMOGRAPHICS

Subject initials : |__|__| |__|__|
First name Family name

Date of birth : |__|__| |__|__|__| |__|__|__|__|
day month year

Gender :
- ☐ Male
- ☐ Female

Race :
- ☐ (WH) White
- ☐ (BL) Black
- ☐ (OR) Oriental
- ☐ (OT) Other, please specify: _____

Height : |__|__|__| cm

Weight : |__|__|__| . |__| kg

Is the subject eligible for the study, according to the criteria listed hereby ?

- ☐ Yes
- ☐ No, please give the corresponding criterion number(s) : _____

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

GENERAL MEDICAL HISTORY / PHYSICAL EXAMINATION

Are you aware of any pre-existing conditions or signs and/or symptoms present in the subject prior to the start of the study ?

☐ No

☐ Yes, please check appropriate box(es) and give diagnosis

			PAST	CURRENT		DIAGNOSIS
____	10	Cutaneous	☐	☐	1	----------
			☐	☐	2	----------
____	5	Eyes	☐	☐	1	----------
			☐	☐	2	----------
____	6	Ears-nose-throat	☐	☐	1	----------
			☐	☐	2	----------
____	2	Cardiovascular	☐	☐	1	----------
			☐	☐	2	----------
____	3	Respiratory	☐	☐	1	----------
			☐	☐	2	----------
____	1	Gastrointestinal	☐	☐	1	----------
			☐	☐	2	----------
____	7	Musculoskeletal	☐	☐	1	----------
			☐	☐	2	----------
____	8	Neurological	☐	☐	1	----------
			☐	☐	2	----------
____	12	Genitourinary	☐	☐	1	----------
			☐	☐	2	----------
____	11	Haematology	☐	☐	1	----------
			☐	☐	2	----------
____	4	Allergies	☐	☐	1	----------
			☐	☐	2	----------
____	9	Endocrine	☐	☐	1	----------
			☐	☐	2	----------
____	99	Other (specify)	☐	☐	1	----------
			☐	☐	2	----------

Please report medication(s) as specified in the protocol and fill in the **Medication** section.

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__|.|__| °C → Route : ☐ Axillary ☐ Rectal

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes ☐ No

STOOL SAMPLE (only for a subset)

Has a stool sample been taken at the day of or 1 day prior to vaccination ?

☐ Yes
☐ No ☐ NA

Has a stool sample been taken at day 7 ± 1 ?

☐ Yes
☐ No ☐ NA

→ *** please fill the stools collection section if any stools have been collected.**

FEEDINGS

Is the child fed with :
☐ breast milk
☐ infant formula
☐ both

Did the child :
☐ receive no food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination but not 30 minutes after vaccination ?
☐ receive food within 30 minutes after vaccination but not 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / Site Route**	**Has the study vaccine been administered according to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please specify (*)*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes ☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

Protocol	Visit	Subject Number
444563/006	VISIT 1	

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	Please fill the **GE Episodes** Section	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0
1
2
3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 2

4 months of age

(49 – 83 days after Visit 1)

DOSE 2

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION / VACCINATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the **Contraindications** as specified in the protocol.

STOOLS COLLECTION

Please fill the stools collection section if any stools have been collected

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 2**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 1 until visit 2 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary
☐ Rectal

LABORATORY TESTS (only for a subset)

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes
☐ No ☐ NA

STOOL SAMPLE (only for a subset)

Has a stool sample been taken at the day of or 1 day prior to vaccination ?

☐ Yes
☐ No ☐ NA

Has a stool sample been taken at day 7 ± 1 ?

☐ Yes
☐ No ☐ NA

→ *** please fill the stools collection section if any stools have been collected.**

FEEDINGS

Is the child fed with : ☐ breast milk
☐ infant formula
☐ both

Did the child :
☐ receive no food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination but not 30 minutes after vaccination ?
☐ receive food within 30 minutes after vaccination but not 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 2**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / Site Route**	**Has the study vaccine been administered according to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please specify (*)*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes ☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	Please fill the **GE Episodes** Section	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0 1 2 3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 3

6 months of age

(49 – 83 days after Visit 2)

DOSE 3

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION / VACCINATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the **Contraindications** as specified in the protocol.

STOOLS COLLECTION

Please fill the stools collection section if any stools have been collected

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 3**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 2 until visit 3 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary
☐ Rectal

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes
☐ No

STOOL SAMPLE

Has a stool sample been taken at the day of or 1 day prior to vaccination ?

☐ Yes
☐ No

Has a stool sample been taken at day 7 ± 1 ?

☐ Yes
☐ No

→ *** please fill the stools collection section if any stools have been collected.**

FEEDINGS

Is the child fed with : ☐ breast milk
☐ infant formula
☐ both

Did the child :
☐ receive no food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination but not 30 minutes after vaccination ?
☐ receive food within 30 minutes after vaccination but not 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 3**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / Site Route**	**Has the study vaccine been administered according to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please check all items*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes ☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes→	Please fill the **GE Episodes** Section	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0 1 2 3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 4

8 months of age

(49 – 83 days after Visit 3)

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION / VACCINATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

Please fill the stools collection section if any stools have been collected

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 4**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 3 until visit 4 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes ☐ No

FINAL VISIT

1 YEAR OF AGE

(160 – 200 days after Visit 3)

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

CONCOMITANT VACCINATION

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected

Protocol		Visit	Date of visit	Subject Number
444563/006		**FINAL VISIT**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period between Visit 4 and Visit 5 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

STOOLS COLLECTION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STOOLS COLLECTION

STOOLS 1	STOOLS 2	STOOLS 3
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 4	**STOOLS 5**	**STOOLS 6**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 7	**STOOLS 8**	**STOOLS 9**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 10	**STOOLS 11**	**STOOLS 12**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 13	**STOOLS 14**	**STOOLS 15**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 16	**STOOLS 17**	**STOOLS 18**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STOOLS COLLECTION (continued)

STOOLS 19	STOOLS 20	STOOLS 21
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 22	**STOOLS 23**	**STOOLS 24**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 25	**STOOLS 26**	**STOOLS 27**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 28	**STOOLS 29**	**STOOLS 30**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 31	**STOOLS 32**	**STOOLS 33**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 34	**STOOLS 35**	**STOOLS 36**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min

GASTROENTERITIS EPISODES

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

CONCOMITANT VACCINATION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administered during the timeframe as specified in the protocol ?

☐ No

☐ Yes, please record concomitant vaccination with trade name and / or generic name, and vaccine administration date.

Trade / Generic Name	**Administration date** day month year
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	
	|__|__||__|__|__||__|__|__|__|
For GSK	

MEDICATION

GlaxoSmithKline Biologicals

MEDICATION ROUTE

CODE	LABEL
EXT	External
ID	Intradermal
IH	Inhalation
IM	Intramuscular
IR	Intraarticular
IT	Intrathecal
IV	Intravenous
NA	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

Protocol				Subject Number
444563/006				|__|__|__|__|__|

MEDICATION

→Any immunosuppressants or other immune-modifying drugs or treatments administered at ANY time during the period starting 30 days prior to the first dose of study vaccine and ending at Visit 4 must be recorded with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment. Any antibiotics administered within 7 days preceding each study vaccine/placebo administration and during the first 7 days after each study vaccine/placebo administration and any antipyretics administered at ANY time during the period starting 30 days prior to the first dose of study vaccine and ending one month (minimum 30 days) after the last dose of study vaccine/placebo must be recorded with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment.

→Any other concomitant medication administered prophylactically in anticipation of reaction to the vaccination must also be recorded with trade name and/or generic name of the medication, total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'

Have any of the above mentioned medications/treatments been administered during study period?

☐ No
☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or check box if continuing at end of study day month year	
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__|__|__|__|__|__|__| End: |__|__|__|__|__|__|__|__|	☐
For GSK					

NON-SERIOUS ADVERSE EVENTS

Protocol				Subject Number
444563/006				|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS

(Please report all **serious adverse events** only on the **Serious Adverse Event (SAE)** form).

Have any **non-serious adverse events** occurred within **42 days** post-vaccination, excluding those recorded on the **Solicited Adverse Events** pages ?

☐ No
☐ Yes, please complete the following table.

AE No.	**AE.1**	**AE.2**	**AE.3**
Description	----------	----------	----------
	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)
For GSK			
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3
Causality In your opinion, did the vaccine possibly contribute to this AE ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Outcome	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown

Protocol				Subject Number
444563/006				|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS (continued)

.

AE No.	**AE.4**	**AE.5**	**AE.6**
Description	----------	----------	----------
	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)
For GSK			
Date Started	|__|__||__|__|__||__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__||__|__|__||__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__||__|__|__||__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol
Date Stopped	|__|__||__|__|__||__|__|__|__| day month year	|__|__||__|__|__||__|__|__|__| day month year	|__|__||__|__|__||__|__|__|__| day month year
Intensity	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3
Causality In your opinion, did the vaccine possibly contribute to this AE ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Outcome	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown

SERIOUS ADVERSE EVENT

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EVENT (SAE)

SAE's MUST BE REPORTED TO GLAXOSMITHKLINE BIOLOGICALS WITHIN 24 HOURS

1. **COMPLETE THE SAE PAGES OPPOSITE.**
   Please complete these pages as fully and accurately as possible in order to minimize the time you spend dealing with data queries.

   If the SAE is still ongoing at the time of reporting, please leave "Outcome" blank and update it later.

2. **PLEASE ENSURE THAT ALL INFORMATION ON THE SAE PAGES IS CONSISTENT WITH THE FOLLOWING OTHER CRF PAGES.**
   - Demographics
   - General Medical History / Physical Examination
   - Vaccine Administration page(s) (for doses administered)
   - Medication
   - Concomitant Vaccination

3. **SIGN AND DATE THE SAE PAGES 2 (AND 3). COMPLETE PAGE 3 OF THE SAE FORM IF NEEDED <u>ONLY</u>.**

4. **PHOTOCOPY THE SAE PAGES (DO NOT SEPARATE THE NCR PAGES) AND FAX THE COPY OF THE SAE PAGES TO:**
   → The study contact
   (see Investigator Site File for appropriate fax number).

   → If no photocopier <u>OR</u> fax is available, please telephone the study contact.

5. **FOR ADDITIONAL INFORMATION, PLEASE CHECK THE "ADDITIONAL INFO" BOX AND FOLLOW THE PROCEDURE EXPLAINED AT POINT 4.**

Protocol	Center	Country	GSK Receipt Date	Subject Number
444563/006	|__|__|__|		|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

SERIOUS ADVERSE EVENT (SAE)

☐ **(1)** Initial report ☐ **(3)** Additional info
☐ **(2)** Additional info ☐ **(4)** Additional info

Subject Demography (1)

Initials: \|__\|__\| First name \|__\|__\| Family name

Date of birth: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

Gender : ☐ Male ☐ Female

Adverse Event *(please print clearly)* (2)

Diagnosis (or signs and symptoms if not known)

_____

_____

_____

For GSK

Date and time started : (3)
(Adverse event first symptoms) \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\| day month year hours min

Date and time stopped : (4)
(If ongoing please leave blank) \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\| day month year hours min

Intensity : (5)
(maximum)
☐ 1
☐ 2
☐ 3

In your opinion, did the vaccine possibly contribute to the SAE : (6)
☐ No
☐ Yes

Outcome : (7)
(maximum)
☐ 1 Recovered
☐ 2 Recovered with sequelae
☐ 3 Ongoing
☐ 4 Died

Action taken with respect to Study Vaccine (8)
☐ None
☐ Vaccination course postponed
☐ Vaccination course stopped

Events after further vaccination (9)
☐ Event reappeared
☐ Event did not reappear
☐ Unknown at this time
☐ Not applicable

♦ **Specify criteria for considering this as a Serious Adverse Event.** (10)
(mark all that apply).

1 ☐ Result in death
→ Autopsy ? ☐ No ☐ Yes
↓
Send autopsy report when available

2 ☐ Life threatening

3 ☐ Result in persistent or significant disability/incapacity

4 ☐ Requires in-patient hospitalization.
Admission date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

5 ☐ Prolongation of existing hospitalization
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| day month year

6 ☐ Congenital anomaly / birth defect in the offspring of a study subject.

7 ☐ "Medically important" event- specify: _____

♦ **Other events (not SAE) to be reported in the same way:**
☐ Cancer

Other possible contributors: (11)
(mark all that apply)
☐ Medical history *(record in section 15)*
☐ Other medication *(record in section 14)*
☐ Protocol required procedure
☐ Other procedure
☐ Lack of efficacy
☐ Erroneous administration
☐ Other, specify : _____

(record additional information in section 19)

Was subject withdrawn due to this specific SAE ? (12)
☐ No
☐ Yes

Protocol				Subject Number
444563/006			**SAE (continued)**	|__|__|__|__|__|

Study vaccine Information **(13)**

Vaccine *(specify mixed or separate)*	Dose No	Lot No	Route / Site	Date
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|

Concomitant medication / vaccination that could have contributed to this SAE **(14)**

Drug / vaccine	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Relevant intercurrent illness & medical history that could have contributed to this SAE **(15)**
(Including allergies)

Condition :	Still present? : No ☐ Yes ☐
Condition :	Still present? : No ☐ Yes ☐

Drug(s) used to treat this SAE **(16)**

Drug	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Surgical treatment for this SAE *(please specify)* **(17)**

Description *(provide a brief narrative description of the SAE including relevant diagnostic findings, lab data & evolution of the events etc…)* **(18)**

Investigator signature Date :	(1) |__|__| |__|__|__| |__|__|__|__| day month year	(2) |__|__| |__|__|__| |__|__|__|__| day month year	(3) |__|__| |__|__|__| |__|__|__|__| day month year	(4) |__|__| |__|__|__| |__|__|__|__| day month year
Please PRINT name:				

For GSK Rixensart	*Signature*	*Please PRINT name*	*Date*
Clinical Development Manager:			|__|__| |__|__|__| |__|__|__|__| day month year

AEGIS Number : \|__\|__\|__\|__\|__\|__\|__\|__\|__\|__\| • \|__\|__\|

Protocol				Subject Number
444563/006			**SAE (continued)**	|__|__|__|__|__|

Comments *(provide further comments concerning the case)* **(19)**

Investigator signature Date :	(1) |__||__|__||__|__|__|__| day month year	(2) |__||__|__||__|__|__|__| day month year	(3) |__||__|__||__|__|__|__| day month year	(4) |__||__|__||__|__|__|__| day month year
Please PRINT name:				

For GSK Rixensart	*Signature*	*Please PRINT name*	*Date*
Clinical Development Manager:			|__|__||__|__|__||__|__|__|__| day month year

AEGIS Number : |__|__|__|__|__|__|__|__|__|__| · |__|__|

STUDY CONCLUSION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STUDY CONCLUSION

Has the code been broken?

☐ No
☐ Yes

Did any elimination criteria become applicable during the study?

☐ No
☐ Yes, please specify: _____

Has the subject dropped out of the study?
(a drop out is a subject who did not come back for the concluding visit foreseen in the protocol.)

☐ No
☐ Yes, please mark the **ONE most appropriate** category for drop out.

- ☐ (SAE) Serious adverse event (complete the **Serious Adverse Event form**).
- ☐ (AEX) Non-Serious adverse event (complete the **Non-serious Adverse Event form**).

  please specify AE N°: _____
- ☐ (PTV) Protocol violation, please specify : _____
- ☐ (CWS) Consent withdrawal, not due to an adverse event.
- ☐ (MIG) Migrated / moved from the study area
- ☐ (LFU) Lost to follow-up.
- ☐ (OTH) Other, please specify : _____

Date of last contact : |__|__| |__|__|__| |__|__|__|__|
day month year

Was the subject in good condition at date of last contact?

☐ No, please give details within the **Adverse Events section.**
☐ Yes

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this case report form, the Non-Serious Adverse Events and Serious Adverse Event sections including any laboratory data (if appropriate) and that all information is complete and accurate.

Date : |__|__| |__|__|__| |__|__|__|__|
day month year

Investigator signature :

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	**SOLICITED SYMPTOMS**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose
- **0**: Normal
- **1**: Cough/runny nose which is easily tolerated
- **2**: Cough/runny nose which interferes with daily activity
- **3**: Cough/runny nose which prevents daily activity

Irritability / fussiness:
- **0**: Behavior as usual
- **1**: Crying more than usual / no effect on normal activity
- **2**: Crying more than usual / interferes with normal activity
- **3**: Crying that cannot be comforted/ prevents normal activity

Loss of appetite:
- 0: Normal
- 1: Eating less than usual / no effect on normal activity
- 2: Eating less than usual / interferes with normal activity
- 3: Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given.

SOLICITED SYMPTOMS	Day 0	Day 1 evening	Day 2 evening	Day 3 evening	Day 4 evening	Day 5 evening	Day 6 evening	Day 7 evening	Day 8 evening	Day 9 evening	Day 10 evening	Day 11 evening	Day 12 evening	Day 13 evening	Day 14 evening	Ongoing after day 14?	Date of last day of symptoms day month year
Date:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____		
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Irritability/fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	**if ongoing after day 14, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET**
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

MEDICATION FOR DIARRHEA
- ☐ None
- ☐ Oral rehydration
- ☐ Other, please specify----------

HOSPITALISATION FOR DIARRHEA :
- ☐ No
- ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__||__|__|__||__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 14**	**DOSE 1**	|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea.

SOLICITED GASTROENTERITIS SYMPTOMS	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__| |__|__|__| |__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	**GASTROENTERITIS EPISODES**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS is defined as presence of diarrhea
DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	**OTHER GENERAL SYMPTOMS AND MEDICATION**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

INTENSITY:

Other general symptoms:

1: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse event which prevents normal, everyday activities. (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten / a day-care center and would cause the parents / guardians to seek medical advice).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis symptoms) Please give details below	Intensity	Start date day month year	End date or check box if continuing day month year	
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

MEDICATION Please fill in below if any medication has been taken since the vaccination **(excluding oral rehydration)**		Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
Trade / generic name	Reason				
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**SOLICITED SYMPTOMS**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose
- **0**: Normal
- **1**: Cough/runny nose which is easily tolerated
- **2**: Cough/runny nose which interferes with daily activity
- **3**: Cough/runny nose which prevents daily activity

Irritability / fussiness:
- **0**: Behavior as usual
- **1**: Crying more than usual / no effect on normal activity
- **2**: Crying more than usual / interferes with normal activity
- **3**: Crying that cannot be comforted/ prevents normal activity

Loss of appetite:
- 0: Normal
- 1: Eating less than usual / no effect on normal activity
- 2: Eating less than usual / interferes with normal activity
- 3: Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given.

SOLICITED SYMPTOMS	Day 0	Day 1 evening	Day 2 evening	Day 3 evening	Day 4 evening	Day 5 evening	Day 6 evening	Day 7 evening	Day 8 evening	Day 9 evening	Day 10 evening	Day 11 evening	Day 12 evening	Day 13 evening	Day 14 evening	Ongoing after day 14?	Date of last day of symptoms day month year
Date:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____		
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|
Irritability/fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	**if ongoing after day 14, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET**
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

MEDICATION FOR DIARRHEA
- ☐ None
- ☐ Oral rehydration
- ☐ Other, please specify----------

HOSPITALISATION FOR DIARRHEA :
- ☐ No
- ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__|/|__|__|__|/|__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 14**	**DOSE 2**	|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea.

SOLICITED GASTROENTERITIS SYMPTOMS	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__| |__|__|__| |__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**GASTROENTERITIS EPISODES**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS is defined as presence of diarrhea.
DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episode of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and/or vomiting and record whether medical treatment was given

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**OTHER GENERAL SYMPTOMS AND MEDICATION**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

INTENSITY:

Other general symptoms:

1: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse event which prevents normal, everyday activities. (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten / a day-care center and would cause the parents / guardians to seek medical advice).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis symptoms) Please give details below	Intensity	Start date day month year	End date or check box if continuing day month year	
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

MEDICATION Please fill in below if any medication has been taken since the vaccination **(excluding oral rehydration)**		Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
Trade / generic name	Reason				
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

Protocol	DIARY CARD	DOSE 3	Subject number
444563/006 (Rota-006)	**SOLICITED SYMPTOMS**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose
- **0**: Normal
- **1**: Cough/runny nose which is easily tolerated
- **2**: Cough/runny nose which interferes with daily activity
- **3**: Cough/runny nose which prevents daily activity

Irritability / fussiness:
- **0**: Behavior as usual
- **1**: Crying more than usual / no effect on normal activity
- **2**: Crying more than usual / interferes with normal activity
- **3**: Crying that cannot be comforted/ prevents normal activity

Loss of appetite:
- 0: Normal
- 1: Eating less than usual / no effect on normal activity
- 2: Eating less than usual / interferes with normal activity
- 3: Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given.

SOLICITED SYMPTOMS	Day 0	Day 1 evening	Day 2 evening	Day 3 evening	Day 4 evening	Day 5 evening	Day 6 evening	Day 7 evening	Day 8 evening	Day 9 evening	Day 10 evening	Day 11 evening	Day 12 evening	Day 13 evening	Day 14 evening	Ongoing after day 14?	Date of last day of symptoms day month year
Date:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____		
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Irritability/fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	**if ongoing after day 14, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET**
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

MEDICATION FOR DIARRHEA
- ☐ None
- ☐ Oral rehydration
- ☐ Other, please specify----------

HOSPITALISATION FOR DIARRHEA :
- ☐ No
- ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__||__|__|__||__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 14**	**DOSE 3**	|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea.

SOLICITED GASTROENTERITIS SYMPTOMS	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__| |__|__|__| |__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD	DOSE 3	Subject number
444563/006 (Rota-006)	**GASTROENTERITIS EPISODES**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS is defined as presence of diarrhea
DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

Protocol	DIARY CARD	DOSE 3	Subject number
444563/006 (Rota-006)	**OTHER GENERAL SYMPTOMS AND MEDICATION**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

INTENSITY:

Other general symptoms:

1: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse event which prevents normal, everyday activities. (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten / a day-care center and would cause the parents / guardians to seek medical advice).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis symptoms) Please give details below	Intensity	Start date day month year	End date or check box if continuing day month year	
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

MEDICATION Please fill in below if any medication has been taken since the vaccination **(excluding oral rehydration)**		Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
Trade / generic name	Reason				
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

Center	Subject identification	Subject Number
|__|__|__|	|__|__| First name |__|__| Family name	|__|__|__|__|__|

CONFIDENTIAL

WORKBOOK

444563/006 (Rota-006)
Amendment 5
Group HRV 2 doses

GlaxoSmithKline Biologicals

Rue de l'institut 89, B – 1330 Rixensart, Belgium
Tel: [redacted] Fax: [redacted]

Version 11.4
Date : October 16, 2002

GENERAL INSTRUCTIONS

Print clearly in **CAPITAL LETTERS** using a **black** fountain or ball-point pen and press firmly so that all copies are legible. Insert the writing board beneath all copies of the form being completed. Fill in the subject number on every page and answer all questions except where otherwise indicated.

Do not write in shaded areas which are qualified **"For GSK"**. Information written in these areas **are not the responsibility of the investigator**.
For each subject's **INITIALS**, please enter the first two letters of the first name and the first two letters of the family name.

ABBREVIATIONS: Abbreviations for medical conditions, clinical events or drug names should not be used. Units and route of administration of medication may be abbreviated. NA: not applicable.

IMPORTANT: Errors should be crossed out with a single line and the alteration made as near to the original as possible.
All alterations must be printed, initialed and dated by the investigator or authorized staff.

DATE

Use the following three-letter abbreviations for each month:

January	=	JAN
February	=	FEB
March	=	MAR
April	=	APR
May	=	MAY
June	=	JUN
July	=	JUL
August	=	AUG
September	=	SEP
October	=	OCT
November	=	NOV
December	=	DEC

Example : |0 1| |J A N| |2 0 0 2| = 1st January 2002
day month year

TIME

Unless specified otherwise, use the 24 hour clock :

Example: |1 5| : |3 0| = 3.30 p.m.
hours min

The **Medication** section, the **Concomitant Vaccination** section, the **Non-Serious Adverse Events** section and the **Serious Adverse Event (SAE)** form must be checked for final assessment at the end of the study.

For all subjects enrolled, please complete the **Conclusion after the first rotavirus season and the Study conclusion** forms.

ADVERSE EVENT DEFINITIONS

INTENSITY FOR SOLICITED SYMPTOMS

Cough/runny nose

0 : Normal
1 : Cough/runny nose which is easily tolerated
2 : Cough/runny nose which interferes with daily activity
3 : Cough/runny nose which prevents daily activity

Irritability/Fussiness

0 : Behavior as usual
1 : Crying more than usual / no effect on normal activity
2 : Crying more than usual / interferes with normal activity
3 : Crying that cannot be comforted / prevents normal activity

Loss of appetite

0 : Normal
1 : Eating less than usual / no effect on normal activity
2 : Eating less than usual / interferes with normal activity
3 : Not eating at all

GASTROENTERITIS EPISODES

Any diarrhea defined as three or more looser than normal stools within a day.

INTENSITY FOR NON-SOLICITED SYMPTOMS

0 : No adverse event.
1 : An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 : An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3 : An adverse event which prevents normal, everyday activities
(In a young child, such an adverse event would, for example, prevent attendance at school/kindergarten/ a day-care center and would cause the parents/guardians to seek medical advice).

ADVERSE EVENT DEFINITIONS

CAUSALITY

In your opinion, did the vaccine(s) possibly contribute to the adverse event?

NO : The adverse event is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the adverse event.

YES: There is a reasonable possibility that the vaccine contributed to the adverse event.

OUTCOME

1 : Recovered
2 : Recovered with sequelae
3 : Ongoing at study conclusion active phase or safety follow-up (whichever is applicable)
4 : Died
5 : Unknown

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that:

1 : results in death
2 : is life threatening
3 : results in persistent or significant disability / incapacity
4 : requires in-patient hospitalization
5 : prolongation of existing hospitalization
6 : is a congenital anomaly / birth defect in the offspring of a study subject
7 : In addition, important medical events (i.e. intussusception) that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not results in hospitalization; or development of drug dependency or drug abuse).

For each serious adverse event, please fill in the **Serious Adverse Event (SAE)** form and contact GlaxoSmithKline within 24 hours (one calendar day).

Although not considered as ‘serious adverse events’, cancers must be reported in the same way as serious adverse events.

GlaxoSmithKline Biologicals

444563/006 (Rota-006) – Amendment 5 – Group HRV 2 doses

FLOW SHEET

Age	**2 months**	**4 months**	**6 months**	**1 year**	***2 years***
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	***END OF 1ST EFFICACY PERIOD***	***END OF 2ND EFFICACY PERIOD***
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 MO 4**	**Post vacc 2 MO 10**	***Post vacc 2 MO 22***
Informed consent	•				
Medical history	•				
Check of inclusion criteria	•				
Check of exclusion criteria	•				
Check of elimination criteria		•	•	•	•
Check of contraindications	•	•	•		
Physical examination	•	•	•	•	•
Pre-vaccination body temperature	•	•	•		
Measure/record height and weight	•	•	•	•	•
Blood sampling	• (1 ml of blood)	• (1 ml of blood in a subset#)	• (3 mls of blood in a subset#)	• (1 ml of blood)	
Randomisation	•				
Stool samples will be collected from a subset (N = 400) on the day of administration of dose 1 and dose 2 and on day 7 following each dose. Stool samples will be collected from a subset (N ~ 200) on the day of administration of dose 3 and on day 7 following dose 3	•	•	•		
Study Vaccine	•	•			
Routine Vaccination	•	•	•		
Daily post-vaccination recording of solicited symptoms (days 0–14) by parents/guardians	•	•			
Collection of stool samples ***if the child is suspected to have gastroenteritis***	•	•	•	•	•
Recording of solicited symptoms, non serious adverse events within 42 days after dose 1, dose 2 and dose 3 (in a subset), by investigator		•	•		

FLOW SHEET (Continued)

Age	**2 months**	**4 months**	**6 months**	**1 year**	***2 years***
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	***END OF 1ST EFFICACY PERIOD***	***END OF 2ND EFFICACY PERIOD***
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 MO 4**	**Post vacc 2 MO 10**	***Post vacc 2 MO 22***
Contact (field visit) every week	◊	◊	◊	◊	◊
Return of GE diary	•	•	•	•	•
GE diary transcription		•	•	•	•
Documentation of routine EPI vaccines	•	•	•	•	•
Recording medication	•	•	•		
Reporting of Serious Adverse Events occurring throughout the study period	•	•	•	•	•
Study Conclusion				•¶	•§

#Subset for immunogenicity evaluation (N = 800)

◊ is used to indicate a study procedure which does not require documentation in the individual eCRFs.

¶For subjects who participate only in the first year of efficacy follow-up
§For subjects who participate in a second year of efficacy follow-up

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed. These intervals determine a subject's evaluability in the according to protocol analyses.

Intervals between study visits* for subjects receiving 2 doses of study vaccine/placebo will be as follows (amended: 3-MAY-2002) **(amended: 20-SEP-2002)**

Interval	**Size of interval**
1 (Visit 1→Visit 2)	49 - 83 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→ ***First efficacy follow-up visit***)	160 - 200 days
4 (First efficacy follow-up visit → Second efficacy follow-up visit)	***335–395 days***

*The date of the previous visit is the reference date.

VISIT 1

6 to 12 weeks of age

DOSE 1

Informed Consent has to be obtained prior to any study procedure

ELIGIBILITY CHECKLIST

INCLUSION CRITERIA

All subjects enrolled must satisfy the following criteria at study entry :

1. A male or female child between, and including 6 and 12 weeks (42-90 days) of age at the time of the first vaccination.
2. Free of obvious health problems as established by medical history and clinical examination before entering into the study.
3. Written informed consent obtained from the parents or guardians of the subject.
4. Born after a gestation period (between 36 and 42 weeks) or a birth weight > 2000g.

EXCLUSION CRITERIA FOR ENROLMENT

The following criteria should be checked at the time of study entry. If any apply at the time of study entry, the subject must not be included in the study :

5. Use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the study vaccine or placebo or planned use during the study period.
6. Planned administration of a vaccine (including routine pediatric vaccines) not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.
7. Planned administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
8. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth. (Topical steroids are allowed.)
9. History of diphtheria, tetanus, pertussis, Hib disease and/ or hepatitis B.
10. Previous vaccination against diphtheria, tetanus, pertussis, and/or Haemophilus influenzae type b.
11. Use of antibiotics within 7 days preceding dose 1 (Warrants deferral of vaccination pending recovery of the subject).
12. Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the GI tract or other serious medical condition as determined by the investigator.
13. Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
14. History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.
15. Acute disease at time of enrollment. (Acute disease is defined as the presence of moderate or severe illness with or without fever i.e. temperature ≥ 37.5°C as measured by an axillary thermometer or ≥ 38.0°C as measured by a rectal thermometer). A temperature greater than or equal to these cut-off warrants deferral of the vaccination pending recovery of the subject. (amended: 12-FEB-2001)
16. Gastroenteritis within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).
17. Household contact with an immunosuppressed individual or pregnant women.
18. Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
19. Previous confirmed occurrence of rotavirus gastroenteritis.

ELIMINATION CRITERIA DURING THE STUDY UP TO VISIT 3

The following criteria should be checked at visits 2 and 3.If any become applicable during the study, the subject will not be required to discontinue the study but may be eliminated from the according-to-protocol analysis.

1. Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
2. Use of antibiotics during the period starting from 7 days before dose 1 and 2 and ending 7 days after.
3. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
4. Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of vaccine(s) and ending 14 days after.
5. Administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
6. Administration of immunoglobulins and/or any blood products during the study period.
7. Confirmed immunosuppressive or immunodeficient condition, including HIV.

ELIMINATION CRITERIA DURING THE STUDY FROM VISIT 3 UNTIL THE STUDY END

The following criteria should be checked at the **follow-up visit at the end of the first efficacy follow-up period and at the end of the second efficacy follow-up period as applicable**. *(amended: 3-MAY-2002)* ***(amended: 20-SEP-2002)***

8. Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
9. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
10. Administration of immunoglobulins and/or any blood products during the study period.
11. Confirmed immunosuppressive or immunodeficient condition, including HIV.

Contraindications to vaccination

SB Biologicals' HRV vaccine or placebo:

The following adverse events constitute absolute contraindications to further administration of human rotavirus vaccine or placebo; if any of these adverse events occur during the study, the subject must not receive additional doses of vaccine or placebo but may continue other study procedures at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event :

- Hypersensitivity reaction due to the vaccine.
- Intussusception.

The following adverse events constitute contraindications to administration of human rotavirus vaccine or placebo at a given point in time; if any one of these adverse events occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol or withdrawn at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event.

- Axillary/rectal temperature ≥37.5°C/38.0°C
- Gastroenteritis within 7 days preceding the study vaccine administration.

DTPw-HB+Hib vaccine:

The following adverse events constitute absolute contraindications or precautions to further administration of DTPw-HB+Hib vaccine; if any of these adverse events occurs during the study, the subject must be withdrawn and must be followed until resolution of the event, as with any adverse event :

Absolute contraindications:

- Known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B or Hib vaccines.
- Encephalopathy (not due to another identifiable cause). This is defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, and/or generalized or focal seizures that persist more than a few hours, with failure to recover within 24 hours. Even though causation by DTP-containing vaccine cannot be established, no subsequent doses of pertussis vaccine should be given.

Precautions:

- *If the following adverse events occur in temporal relation to DTPw-HB+Hib vaccine administration, the decision to administer additional doses of DTPw-HB+Hib vaccine should be carefully considered:*
- Fever ≥ 40.5°C/≥ 40.0°C (rectal/axillary temperature) within 48 hours of vaccination not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting >3 hours, occurring within 48 hours of vaccination.
- Seizures with or without fever occurring within 3 days of vaccination.

Protocol	Center	Visit	Date of visit	Subject Number
444563/006	|__|__|__|	**VISIT 1**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date : |__|__| |__|__|__| |__|__|__|__|
day month year

DEMOGRAPHICS

Subject initials : |__|__| |__|__|
First name Family name

Date of birth : |__|__| |__|__|__| |__|__|__|__|
day month year

Gender : ☐ Male
☐ Female

Race : ☐ (WH) White
☐ (BL) Black
☐ (OR) Oriental
☐ (OT) Other, please specify: _____

Height : |__|__|__| cm

Weight : |__|__|__| . |__| kg

Is the subject eligible for the study, according to the criteria listed hereby ?

☐ Yes
☐ No, please give the corresponding criterion number(s) : _____

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

GENERAL MEDICAL HISTORY / PHYSICAL EXAMINATION

Are you aware of any pre-existing conditions or signs and/or symptoms present in the subject prior to the start of the study ?

☐ No

☐ Yes, please check appropriate box(es) and give diagnosis

			PAST	CURRENT	DIAGNOSIS
____	10	Cutaneous	☐	☐	1 ----------
			☐	☐	2 ----------
____	5	Eyes	☐	☐	1 ----------
			☐	☐	2 ----------
____	6	Ears-nose-throat	☐	☐	1 ----------
			☐	☐	2 ----------
____	2	Cardiovascular	☐	☐	1 ----------
			☐	☐	2 ----------
____	3	Respiratory	☐	☐	1 ----------
			☐	☐	2 ----------
____	1	Gastrointestinal	☐	☐	1 ----------
			☐	☐	2 ----------
____	7	Musculoskeletal	☐	☐	1 ----------
			☐	☐	2 ----------
____	8	Neurological	☐	☐	1 ----------
			☐	☐	2 ----------
____	12	Genitourinary	☐	☐	1 ----------
			☐	☐	2 ----------
____	11	Haematology	☐	☐	1 ----------
			☐	☐	2 ----------
____	4	Allergies	☐	☐	1 ----------
			☐	☐	2 ----------
____	9	Endocrine	☐	☐	1 ----------
			☐	☐	2 ----------
____	99	Other (specify)	☐	☐	1 ----------
			☐	☐	2 ----------

Please report medication(s) as specified in the protocol and fill in the **Medication** section.

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary ☐ Rectal

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes ☐ No

STOOL SAMPLE (only for a subset)

Has a stool sample been taken at the day of or 1 day prior to vaccination ?

☐ Yes
☐ No ☐ NA

Has a stool sample been taken at day 7 ± 1 ?

☐ Yes
☐ No ☐ NA

→ *** please fill the stools collection section if any stools have been collected.**

FEEDINGS

Is the child fed with :
☐ breast milk
☐ infant formula
☐ both

Did the child :
☐ receive no food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination but not 30 minutes after vaccination ?
☐ receive food within 30 minutes after vaccination but not 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / Site Route**	**Has the study vaccine been administered according to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please specify (*)*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes ☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	Please fill the **GE Episodes** Section	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0
1
2
3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 2

4 months of age

(49 – 83 days after Visit 1)

DOSE 2

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION / VACCINATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the **Contraindications** as specified in the protocol.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 2**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 1 until visit 2 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary
☐ Rectal

LABORATORY TESTS (only for a subset)

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes
☐ No ☐ NA

STOOL SAMPLE (only for a subset)

Has a stool sample been taken at the day of or 1 day prior to vaccination ?

☐ Yes
☐ No ☐ NA

Has a stool sample been taken at day 7 ± 1 ?

☐ Yes
☐ No ☐ NA

→ *** please fill the stools collection section if any stools have been collected.**

FEEDINGS

Is the child fed with : ☐ breast milk
☐ infant formula
☐ both

Did the child :
☐ receive no food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination but not 30 minutes after vaccination ?
☐ receive food within 30 minutes after vaccination but not 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 2**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / Site Route**	**Has the study vaccine been administered according to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please specify (*)*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes ☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	Please fill the **GE Episodes** Section	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0
1
2
3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 3

6 months of age

(49 – 83 days after Visit 2)

DOSE 3

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION / VACCINATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the **Contraindications** as specified in the protocol.

STOOLS COLLECTION

Please fill the stools collection section if any stools have been collected

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 3**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 2 until visit 3 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary
☐ Rectal

LABORATORY TESTS (only for a subset)

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes
☐ No ☐ NA

Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

END OF 1st
EFFICACY PERIOD

1 YEAR OF AGE
(160 – 200 days after Visit 3)

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

SERIOUS ADVERSE EVENTS

→ Please report serious adverse events as specified in the protocol and fill in the **Serious Event (SAE)** form, as appropriate.

CONCOMITANT VACCINATION

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected

Protocol			Date of visit	Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period between Visit 3 and the end of the 1st efficacy period ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

LABORATORY TESTS

Minimum of 3 mls of whole blood for the subject in the immuno subset and a minimum of 1ml for the other subjects who received two doses of study vaccine or placebo.

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes
☐ No

STOOLS

COLLECTION

END OF 1st
EFFICACY PERIOD

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

STOOLS COLLECTION

STOOLS 1	STOOLS 2	STOOLS 3
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 4	**STOOLS 5**	**STOOLS 6**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 7	**STOOLS 8**	**STOOLS 9**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 10	**STOOLS 11**	**STOOLS 12**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 13	**STOOLS 14**	**STOOLS 15**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 16	**STOOLS 17**	**STOOLS 18**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

STOOLS COLLECTION (continued)

STOOLS 19	STOOLS 20	STOOLS 21
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 22	**STOOLS 23**	**STOOLS 24**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 25	**STOOLS 26**	**STOOLS 27**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 28	**STOOLS 29**	**STOOLS 30**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 31	**STOOLS 32**	**STOOLS 33**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 34	**STOOLS 35**	**STOOLS 36**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min

GASTROENTERITIS EPISODES

END OF 1st EFFICACY PERIOD

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

CONCOMITANT VACCINATION

END OF 1st EFFICACY PERIOD

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administered during the timeframe as specified in the protocol ?

☐ No

☐ Yes, please record concomitant vaccination with trade name and / or generic name, and vaccine administration date.

Trade / Generic Name	**Administration date** day month year
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	

CONCOMITANT MEDICATION

END OF 1st EFFICACY PERIOD

GlaxoSmithKline Biologicals

MEDICATION ROUTE

CODE	LABEL
EXT	External
ID	Intradermal
IH	Inhalation
IM	Intramuscular
IR	Intraarticular
IT	Intrathecal
IV	Intravenous
NA	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

MEDICATION

→Any immunosuppressants or other immune-modifying drugs or treatments administered at ANY time during the period starting 30 days prior to the first dose of study vaccine and ending at Visit 3 must be recorded with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment. Any antibiotics administered within 7 days preceding each study vaccine/placebo administration and during the first 7 days after each study vaccine/placebo administration and any antipyretics administered at ANY time during the period starting 30 days prior to the first dose of study vaccine and ending one month (minimum 30 days) after the last dose of study vaccine/placebo must be recorded with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment.

→Any other concomitant medication administered prophylactically in anticipation of reaction to the vaccination must also be recorded with trade name and/or generic name of the medication, total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'

Have any of the above mentioned medications/treatments been administered during study period?

☐ No
☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or check box if continuing at end of study day month year	
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					

NON-SERIOUS ADVERSE EVENTS

END OF 1st EFFICACY PERIOD

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS

(Please report all **serious adverse events** only on the **Serious Adverse Event (SAE)** form).

Have any **non-serious adverse events** occurred within **42 days** post-vaccination, excluding those recorded on the **Solicited Adverse Events** pages ?

☐ No
☐ Yes, please complete the following table.

AE No.	**AE.1**	**AE.2**	**AE.3**
Description	----------	----------	----------
	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)
For GSK			
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3
Causality In your opinion, did the vaccine possibly contribute to this AE ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Outcome	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS (continued)

.

AE No.	**AE.4**	**AE.5**	**AE.6**
Description	----------	----------	----------
	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)
For GSK			
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3
Causality In your opinion, did the vaccine possibly contribute to this AE ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Outcome	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown

SERIOUS ADVERSE EVENT

END OF 1st EFFICACY PERIOD

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EVENT (SAE)

SAE's MUST BE REPORTED TO GLAXOSMITHKLINE BIOLOGICALS WITHIN 24 HOURS

1. **COMPLETE THE SAE PAGES OPPOSITE.**
   Please complete these pages as fully and accurately as possible in order to minimize the time you spend dealing with data queries.

   If the SAE is still ongoing at the time of reporting, please leave "Outcome" blank and update it later.

2. **PLEASE ENSURE THAT ALL INFORMATION ON THE SAE PAGES IS CONSISTENT WITH THE FOLLOWING OTHER CRF PAGES.**
   - Demographics
   - General Medical History / Physical Examination
   - Vaccine Administration page(s) (for doses administered)
   - Medication
   - Concomitant Vaccination

3. **SIGN AND DATE THE SAE PAGES 2 (AND 3). COMPLETE PAGE 3 OF THE SAE FORM IF NEEDED <u>ONLY</u>.**

4. **PHOTOCOPY THE SAE PAGES (DO NOT SEPARATE THE NCR PAGES) AND FAX THE COPY OF THE SAE PAGES TO:**
   → The study contact
   (see Investigator Site File for appropriate fax number).

   → If no photocopier <u>OR</u> fax is available, please telephone the study contact.

5. **FOR ADDITIONAL INFORMATION, PLEASE CHECK THE "ADDITIONAL INFO" BOX AND FOLLOW THE PROCEDURE EXPLAINED AT POINT 4.**

Protocol	Center	Country	GSK Receipt Date	Subject Number
444563/006	|__|__|__|		|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

SERIOUS ADVERSE EVENT (SAE)

END OF 1st EFFICACY PERIOD

☐ **(1)** Initial report ☐ **(3)** Additional info
☐ **(2)** Additional info ☐ **(4)** Additional info

Subject Demography (1)

Initials: \|__\|__\| \|__\|__\|
First name Family name

Date of birth: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

Gender : ☐ Male ☐ Female

Adverse Event *(please print clearly)* (2)

Diagnosis (or signs and symptoms if not known)

_____

_____

_____

For GSK

Date and time started : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\| (3)
(Adverse event first symptoms) day month year hours min

Date and time stopped : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\| (4)
(If ongoing please leave blank) day month year hours min

Intensity : (5)
(maximum)
☐ 1
☐ 2
☐ 3

In your opinion, did the vaccine possibly contribute to the SAE : (6)
☐ No
☐ Yes

Outcome : (7)
(maximum)
☐ 1 Recovered
☐ 2 Recovered with sequelae
☐ 3 Ongoing
☐ 4 Died

Action taken with respect to Study Vaccine (8)
☐ None
☐ Vaccination course postponed
☐ Vaccination course stopped

Events after further vaccination (9)
☐ Event reappeared
☐ Event did not reappear
☐ Unknown at this time
☐ Not applicable

♦ **Specify criteria for considering this as a Serious Adverse Event.** (10)
(mark all that apply).

1 ☐ Result in death
→ Autopsy ? ☐ No ☐ Yes
↓
Send autopsy report when available

2 ☐ Life threatening

3 ☐ Result in persistent or significant disability/incapacity

4 ☐ Requires in-patient hospitalization.
Admission date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

5 ☐ Prolongation of existing hospitalization
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

6 ☐ Congenital anomaly / birth defect in the offspring of a study subject.

7 ☐ "Medically important" event- specify: _____

♦ **Other events (not SAE) to be reported in the same way:**
☐ Cancer

Other possible contributors: (11)
(mark all that apply)
☐ Medical history *(record in section 15)*
☐ Other medication *(record in section 14)*
☐ Protocol required procedure
☐ Other procedure
☐ Lack of efficacy
☐ Erroneous administration
☐ Other, specify : _____

(record additional information in section 19)

Was subject withdrawn due to this specific SAE ? (12)
☐ No
☐ Yes

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**	**SAE (continued)**	|__|__|__|__|__|

Study vaccine Information **(13)**

Vaccine *(specify mixed or separate)*	Dose No	Lot No	Route / Site	Date
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|

Concomitant medication / vaccination that could have contributed to this SAE **(14)**

Drug / vaccine	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Relevant intercurrent illness & medical history that could have contributed to this SAE **(15)**
(Including allergies)

Condition :	Still present? : No ☐ Yes ☐
Condition :	Still present? : No ☐ Yes ☐

Drug(s) used to treat this SAE **(16)**

Drug	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Surgical treatment for this SAE *(please specify)* **(17)**

Description *(provide a brief narrative description of the SAE including relevant diagnostic findings, lab data & evolution of the events etc…)* **(18)**

Investigator signature Date :	(1) |__|__| |__|__|__| |__|__|__|__| day month year	(2) |__|__| |__|__|__| |__|__|__|__| day month year	(3) |__|__| |__|__|__| |__|__|__|__| day month year	(4) |__|__| |__|__|__| |__|__|__|__| day month year
Please PRINT name:				

For GSK Rixensart	*Signature*	*Please PRINT name*	*Date*
Clinical Development Manager:			|__|__| |__|__|__| |__|__|__|__| day month year

AEGIS Number : |__|__|__|__|__|__|__|__|__|__| . |__|__|

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**	**SAE (continued)**	|__|__|__|__|__|

Comments *(provide further comments concerning the case)* **(19)**

Investigator signature Date :	(1) |_|_| |_|_|_|_| |_|_|_|_| day month year	(2) |_|_| |_|_|_|_| |_|_|_|_| day month year	(3) |_|_| |_|_|_|_| |_|_|_|_| day month year	(4) |_|_| |_|_|_|_| |_|_|_|_| day month year
Please PRINT name:				

For GSK Rixensart	*Signature*	*Please PRINT name*	*Date*
Clinical Development Manager:			|_|_| |_|_|_|_| |_|_|_|_| day month year

AEGIS Number : \|_\|_\|_\|_\|_\|_\|_\|_\|_\|_\| · \|_\|_\|

STUDY

CONCLUSION

END OF 1st
EFFICACY PERIOD

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STUDY CONCLUSION AT THE END OF THE 1st EFFICACY FU PERIOD

Has the code been broken?

☐ No
☐ Yes

Did any elimination criteria become applicable during the study?

☐ No
☐ Yes, please specify: _____

Has the subject dropped out of the study?
(a drop out is a subject who did not come back for the concluding visit foreseen in the protocol.)

☐ No
☐ Yes, please mark the **ONE most appropriate** category for drop out.

- ☐ (SAE) Serious adverse event (complete the **Serious Adverse Event form**).
- ☐ (AEX) Non-Serious adverse event (complete the **Non-serious Adverse Event form**).

  please specify AE N°: _____
- ☐ (PTV) Protocol violation, please specify : _____
- ☐ (CWS) Consent withdrawal, not due to an adverse event.
- ☐ (MIG) Migrated / moved from the study area
- ☐ (LFU) Lost to follow-up.
- ☐ (OTH) Other, please specify : _____

Date of last contact : |__|__| |__|__|__| |__|__|__|__|
day month year

Was the subject in good condition at date of last contact?

☐ No, please give details within the **Adverse Events section.**
☐ Yes

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this case report form, the Non-Serious Adverse Events and Serious Adverse Event sections including any laboratory data (if appropriate) and that all information is complete and accurate.

Date : |__|__| |__|__|__| |__|__|__|__|
day month year

Investigator signature :

END OF 2nd

EFFICACY PERIOD

2 YEARS OF AGE

(335 – 395 days after end of 1st efficacy follow-up visit)

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

SERIOUS ADVERSE EVENTS

→ Please report serious adverse events as specified in the protocol and fill in the **Serious Event (SAE)** form, as appropriate.

CONCOMITANT VACCINATION

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected

Protocol			Date of visit	Subject Number
444563/006		**END OF 2nd EFFICACY PERIOD**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period between the end of the 1st efficacy period and the end of the 2nd efficacy period ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

STOOLS COLLECTION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STOOLS COLLECTION

STOOLS 1	STOOLS 2	STOOLS 3
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 4	**STOOLS 5**	**STOOLS 6**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 7	**STOOLS 8**	**STOOLS 9**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 10	**STOOLS 11**	**STOOLS 12**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 13	**STOOLS 14**	**STOOLS 15**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 16	**STOOLS 17**	**STOOLS 18**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STOOLS COLLECTION (continued)

STOOLS 19	STOOLS 20	STOOLS 21
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 22	**STOOLS 23**	**STOOLS 24**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 25	**STOOLS 26**	**STOOLS 27**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 28	**STOOLS 29**	**STOOLS 30**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 31	**STOOLS 32**	**STOOLS 33**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 34	**STOOLS 35**	**STOOLS 36**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min

GASTROENTERITIS EPISODES

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

CONCOMITANT VACCINATION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administeredbetween the end of the 1st efficacy period and the end of the 2nd efficacy period ?

☐ No
☐ Yes, please record concomitant vaccination with trade name and / or generic name, and vaccine administration date.

Trade / Generic Name	**Administration date** day month year
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	

SERIOUS ADVERSE EVENT

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EVENT (SAE)

SAE's MUST BE REPORTED TO GLAXOSMITHKLINE BIOLOGICALS WITHIN 24 HOURS

1. **COMPLETE THE SAE PAGES OPPOSITE.**
   Please complete these pages as fully and accurately as possible in order to minimize the time you spend dealing with data queries.

   If the SAE is still ongoing at the time of reporting, please leave "Outcome" blank and update it later.

2. **PLEASE ENSURE THAT ALL INFORMATION ON THE SAE PAGES IS CONSISTENT WITH THE FOLLOWING OTHER CRF PAGES.**
   - Demographics
   - General Medical History / Physical Examination
   - Vaccine Administration page(s) (for doses administered)
   - Medication
   - Concomitant Vaccination

3. **SIGN AND DATE THE SAE PAGES 2 (AND 3). COMPLETE PAGE 3 OF THE SAE FORM IF NEEDED <u>ONLY</u>.**

4. **PHOTOCOPY THE SAE PAGES (DO NOT SEPARATE THE NCR PAGES) AND FAX THE COPY OF THE SAE PAGES TO:**
   → The study contact
   (see Investigator Site File for appropriate fax number).

   → If no photocopier <u>OR</u> fax is available, please telephone the study contact.

5. **FOR ADDITIONAL INFORMATION, PLEASE CHECK THE "ADDITIONAL INFO" BOX AND FOLLOW THE PROCEDURE EXPLAINED AT POINT 4.**

Protocol	Center	Country	GSK Receipt Date	Subject Number
444563/006	|__|__|__|		|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

SERIOUS ADVERSE EVENT (SAE)

☐ **(1)** Initial report ☐ **(3)** Additional info
☐ **(2)** Additional info ☐ **(4)** Additional info

Subject Demography (1)

Initials: \|__\|__\| \|__\|__\|
First name Family name

Date of birth: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

Gender : ☐ Male ☐ Female

Adverse Event *(please print clearly)* (2)

Diagnosis (or signs and symptoms if not known)

_____

_____

_____

For GSK

Date and time started : (3)
(Adverse event first symptoms) \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\|
day month year hours min

Date and time stopped : (4)
(If ongoing please leave blank) \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\|
day month year hours min

Intensity : (5)
(maximum)
☐ 1
☐ 2
☐ 3

In your opinion, did the vaccine possibly contribute to the SAE : (6)
☐ No
☐ Yes

Outcome : (7)
(maximum)
☐ 1 Recovered
☐ 2 Recovered with sequelae
☐ 3 Ongoing
☐ 4 Died

Action taken with respect to Study Vaccine (8)
☐ None
☐ Vaccination course postponed
☐ Vaccination course stopped

Events after further vaccination (9)
☐ Event reappeared
☐ Event did not reappear
☐ Unknown at this time
☐ Not applicable

♦ **Specify criteria for considering this as a Serious Adverse Event.** (10)
(mark all that apply).

1 ☐ Result in death
→ Autopsy ? ☐ No ☐ Yes
↓
Send autopsy report when available

2 ☐ Life threatening

3 ☐ Result in persistent or significant disability/incapacity

4 ☐ Requires in-patient hospitalization.
Admission date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

5 ☐ Prolongation of existing hospitalization
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

6 ☐ Congenital anomaly / birth defect in the offspring of a study subject.

7 ☐ "Medically important" event- specify: _____

♦ **Other events (not SAE) to be reported in the same way:**
☐ Cancer

Other possible contributors: (11)
(mark all that apply)
☐ Medical history *(record in section 15)*
☐ Other medication *(record in section 14)*
☐ Protocol required procedure
☐ Other procedure
☐ Lack of efficacy
☐ Erroneous administration
☐ Other, specify : _____

(record additional information in section 19)

Was subject withdrawn due to this specific SAE ? (12)
☐ No
☐ Yes

Protocol				Subject Number
444563/006			**SAE (continued)**	|__|__|__|__|__|

Study vaccine Information **(13)**

Vaccine *(specify mixed or separate)*	Dose No	Lot No	Route / Site	Date
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|

Concomitant medication / vaccination that could have contributed to this SAE **(14)**

Drug / vaccine	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Relevant intercurrent illness & medical history that could have contributed to this SAE **(15)**
(Including allergies)

Condition :	Still present? : No ☐ Yes ☐
Condition :	Still present? : No ☐ Yes ☐

Drug(s) used to treat this SAE **(16)**

Drug	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Surgical treatment for this SAE *(please specify)* **(17)**

Description *(provide a brief narrative description of the SAE including relevant diagnostic findings, lab data & evolution of the events etc…)* **(18)**

Investigator signature Date :	(1) |__|__| |__|__|__| |__|__|__|__| day month year	(2) |__|__| |__|__|__| |__|__|__|__| day month year	(3) |__|__| |__|__|__| |__|__|__|__| day month year	(4) |__|__| |__|__|__| |__|__|__|__| day month year
Please PRINT name:				

For GSK Rixensart	*Signature*	*Please PRINT name*	*Date*
Clinical Development Manager:			|__|__| |__|__|__| |__|__|__|__| day month year

AEGIS Number : \|__\|__\|__\|__\|__\|__\|__\|__\|__\|__\| . \|__\|__\|

Protocol				Subject Number
444563/006			**SAE (continued)**	|__|__|__|__|__|

Comments *(provide further comments concerning the case)* **(19)**

Investigator signature Date :	(1) |_|_| |_|_|_|_| |_|_|_|_|_|_| day month year	(2) |_|_| |_|_|_|_| |_|_|_|_|_|_| day month year	(3) |_|_| |_|_|_|_| |_|_|_|_|_|_| day month year	(4) |_|_| |_|_|_|_| |_|_|_|_|_|_| day month year
Please PRINT name:				

For GSK Rixensart	*Signature*	*Please PRINT name*	*Date*
Clinical Development Manager:			|_|_| |_|_|_|_| |_|_|_|_|_|_| day month year

AEGIS Number : |_|_|_|_|_|_|_|_|_|_| · |_|_|

STUDY

CONCLUSION

AT THE END OF THE
2nd EFFICACY FU PERIOD

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STUDY CONCLUSION AT THE END OF THE 2nd EFFICACY FU PERIOD

Has the code been broken?

☐ No
☐ Yes

Did any elimination criteria become applicable during the study?

☐ No
☐ Yes, please specify: _____

Has the subject dropped out of the study?
(a drop out is a subject who did not come back for the concluding visit foreseen in the protocol.)

☐ No
☐ Yes, please mark the **ONE most appropriate** category for drop out.

- ☐ (SAE) Serious adverse event (complete the **Serious Adverse Event form**).
- ☐ (AEX) Non-Serious adverse event (complete the **Non-serious Adverse Event form**).

  please specify AE N°: _____
- ☐ (PTV) Protocol violation, please specify : _____
- ☐ (CWS) Consent withdrawal, not due to an adverse event.
- ☐ (MIG) Migrated / moved from the study area
- ☐ (LFU) Lost to follow-up.
- ☐ (OTH) Other, please specify : _____

Date of last contact : |__|__| |__|__|__| |__|__|__|__|
day month year

Was the subject in good condition at date of last contact?

☐ No, please give details within the **Adverse Events section.**
☐ Yes

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this case report form, the Non-Serious Adverse Events and Serious Adverse Event sections including any laboratory data (if appropriate) and that all information is complete and accurate.

Date : |__|__| |__|__|__| |__|__|__|__|
day month year

Investigator signature :

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	**SOLICITED SYMPTOMS**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose
- **0**: Normal
- **1**: Cough/runny nose which is easily tolerated
- **2**: Cough/runny nose which interferes with daily activity
- **3**: Cough/runny nose which prevents daily activity

Irritability / fussiness:
- **0**: Behavior as usual
- **1**: Crying more than usual / no effect on normal activity
- **2**: Crying more than usual / interferes with normal activity
- **3**: Crying that cannot be comforted/ prevents normal activity

Loss of appetite:
- 0: Normal
- 1: Eating less than usual / no effect on normal activity
- 2: Eating less than usual / interferes with normal activity
- 3: Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given.

SOLICITED SYMPTOMS	Day 0	Day 1 evening	Day 2 evening	Day 3 evening	Day 4 evening	Day 5 evening	Day 6 evening	Day 7 evening	Day 8 evening	Day 9 evening	Day 10 evening	Day 11 evening	Day 12 evening	Day 13 evening	Day 14 evening	Ongoing after day 14?	Date of last day of symptoms day month year
Date:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____		
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Irritability/fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	**if ongoing after day 14, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET**
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

MEDICATION FOR DIARRHEA
- ☐ None
- ☐ Oral rehydration
- ☐ Other, please specify----------

HOSPITALISATION FOR DIARRHEA :
- ☐ No
- ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__||__|__|__||__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 14**	**DOSE 1**	|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea.

SOLICITED GASTROENTERITIS SYMPTOMS	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__| |__|__|__| |__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	**GASTROENTERITIS EPISODES**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS is defined as presence of diarrhea
DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	**OTHER GENERAL SYMPTOMS AND MEDICATION**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

INTENSITY:

Other general symptoms:

1: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse event which prevents normal, everyday activities. (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten / a day-care center and would cause the parents / guardians to seek medical advice).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis symptoms) Please give details below	Intensity	Start date day month year	End date or check box if continuing day month year	
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

MEDICATION Please fill in below if any medication has been taken since the vaccination **(excluding oral rehydration)**		Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
Trade / generic name	Reason				
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**SOLICITED SYMPTOMS**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose	***Irritability / fussiness:***	***Loss of appetite:***
0: Normal	**0**: Behavior as usual	0: Normal
1: Cough/runny nose which is easily tolerated	**1**: Crying more than usual / no effect on normal activity	1: Eating less than usual / no effect on normal activity
2: Cough/runny nose which interferes with daily activity	**2**: Crying more than usual / interferes with normal activity	2: Eating less than usual / interferes with normal activity
3: Cough/runny nose which prevents daily activity	**3**: Crying that cannot be comforted/ prevents normal activity	3: Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given.

SOLICITED SYMPTOMS	Day 0	Day 1 evening	Day 2 evening	Day 3 evening	Day 4 evening	Day 5 evening	Day 6 evening	Day 7 evening	Day 8 evening	Day 9 evening	Day 10 evening	Day 11 evening	Day 12 evening	Day 13 evening	Day 14 evening	Ongoing after day 14?	Date of last day of symptoms day month year
Date:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____		
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Irritability/fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	**if ongoing after day 14, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET**
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

MEDICATION FOR DIARRHEA

☐ None
☐ Oral rehydration
☐ Other, please specify----------

HOSPITALISATION FOR DIARRHEA :

☐ No
☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__|/|__|__|__|/|__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 14**	**DOSE 2**	|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea.

SOLICITED GASTROENTERITIS SYMPTOMS	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__| |__|__|__| |__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**GASTROENTERITIS EPISODES**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS is defined as presence of diarrhea.
DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episode of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and/or vomiting and record whether medical treatment was given

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**OTHER GENERAL SYMPTOMS AND MEDICATION**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

INTENSITY:

Other general symptoms:

1: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse event which prevents normal, everyday activities. (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten / a day-care center and would cause the parents / guardians to seek medical advice).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis symptoms) Please give details below	Intensity	Start date day month year	End date or check box if continuing day month year	
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

MEDICATION Please fill in below if any medication has been taken since the vaccination **(excluding oral rehydration)**		Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
Trade / generic name	Reason				
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

Center	Subject identification	Subject Number
|__|__|__|	|__|__| First name |__|__| Family name	|__|__|__|__|__|

CONFIDENTIAL

WORKBOOK

444563/006 (Rota-006)
Amendment 5
Group HRV 3 doses

GlaxoSmithKline Biologicals

Rue de l'institut 89, B – 1330 Rixensart, Belgium
Tel: [redacted] Fax: [redacted]

Version 11.4
Date : October 16, 2002

GENERAL INSTRUCTIONS

Print clearly in **CAPITAL LETTERS** using a **black** fountain or ball-point pen and press firmly so that all copies are legible. Insert the writing board beneath all copies of the form being completed. Fill in the subject number on every page and answer all questions except where otherwise indicated.

Do not write in shaded areas which are qualified **"For GSK"**. Information written in these areas **are not the responsibility of the investigator**.
For each subject's **INITIALS**, please enter the first two letters of the first name and the first two letters of the family name.

ABBREVIATIONS: Abbreviations for medical conditions, clinical events or drug names should not be used. Units and route of administration of medication may be abbreviated. NA: not applicable.

IMPORTANT: Errors should be crossed out with a single line and the alteration made as near to the original as possible.
All alterations must be printed, initialed and dated by the investigator or authorized staff.

DATE

Use the following three-letter abbreviations for each month:

January	=	JAN
February	=	FEB
March	=	MAR
April	=	APR
May	=	MAY
June	=	JUN
July	=	JUL
August	=	AUG
September	=	SEP
October	=	OCT
November	=	NOV
December	=	DEC

Example : |0 1| |J A N| |2 0 0 2| = 1st January 2002
day month year

TIME

Unless specified otherwise, use the 24 hour clock :

Example: |1 5| : |3 0| = 3.30 p.m.
hours min

The **Medication** section, the **Concomitant Vaccination** section, the **Non-Serious Adverse Events** section and the **Serious Adverse Event (SAE)** form must be checked for final assessment at the end of the study.

For all subjects enrolled, please complete the **Conclusion after the first rotavirus season and the Study conclusion** forms.

ADVERSE EVENT DEFINITIONS

INTENSITY FOR SOLICITED SYMPTOMS

Cough/runny nose

0 : Normal
1 : Cough/runny nose which is easily tolerated
2 : Cough/runny nose which interferes with daily activity
3 : Cough/runny nose which prevents daily activity

Irritability/Fussiness

0 : Behavior as usual
1 : Crying more than usual / no effect on normal activity
2 : Crying more than usual / interferes with normal activity
3 : Crying that cannot be comforted / prevents normal activity

Loss of appetite

0 : Normal
1 : Eating less than usual / no effect on normal activity
2 : Eating less than usual / interferes with normal activity
3 : Not eating at all

GASTROENTERITIS EPISODES

Any diarrhea defined as three or more looser than normal stools within a day.

INTENSITY FOR NON-SOLICITED SYMPTOMS

0 : No adverse event.
1 : An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 : An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3 : An adverse event which prevents normal, everyday activities
(In a young child, such an adverse event would, for example, prevent attendance at school/kindergarten/ a day-care center and would cause the parents/guardians to seek medical advice).

ADVERSE EVENT DEFINITIONS

CAUSALITY

In your opinion, did the vaccine(s) possibly contribute to the adverse event?

NO : The adverse event is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the adverse event.

YES: There is a reasonable possibility that the vaccine contributed to the adverse event.

OUTCOME

1 : Recovered
2 : Recovered with sequelae
3 : Ongoing at study conclusion active phase or safety follow-up (whichever is applicable)
4 : Died
5 : Unknown

SERIOUS ADVERSE EVENT

A serious adverse event is any untoward medical occurrence that:

1 : results in death
2 : is life threatening
3 : results in persistent or significant disability / incapacity
4 : requires in-patient hospitalization
5 : prolongation of existing hospitalization
6 : is a congenital anomaly / birth defect in the offspring of a study subject
7 : In addition, important medical events (i.e. intussusception) that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not results in hospitalization; or development of drug dependency or drug abuse).

For each serious adverse event, please fill in the **Serious Adverse Event (SAE)** form and contact GlaxoSmithKline within 24 hours (one calendar day).

Although not considered as ‘serious adverse events’, cancers must be reported in the same way as serious adverse events.

GlaxoSmithKline Biologicals

444563/006 (Rota-006) – Amendment 5 – Group HRV 3 doses

FLOW SHEET

Age	**2 months**	**4 months**	**6 months**	**8 months**	**1 year**	***2 years***
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4 DOSE 3 SUBSET ONLY***	***END OF 1ST EFFICACY PERIOD***	***END OF 2ND EFFICACY PERIOD***
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 MO 4**	**Post vacc 3 MO 6**	**Post vacc 2 MO 10**	***Post vacc 2 MO 22***
Informed consent	•					
Medical history	•					
Check of inclusion criteria	•					
Check of exclusion criteria	•					
Check of elimination criteria		•	•	•	•	•
Check of contraindications	•	•	•			
Physical examination	•	•	•	•	•	•
Pre-vaccination body temperature	•	•	•			
Measure/record height and weight	•	•	•	•	•	•
Blood sampling	• (1 ml of blood)	• (1 ml of blood in a subset#)	• (1 ml of blood)	• (3 mls of blood)	• (3 mls of blood in a subset#)	
Randomisation	•					
Stool samples will be collected from a subset (N = 400) on the day of administration of dose 1 and dose 2 and on day 7 following each dose. Stool samples will be collected from a subset (N ~ 200) on the day of administration of dose 3 and on day 7 following dose 3	•	•	•			
Study Vaccine	•	•	• (dose 3 subset*)			
Routine Vaccination	•	•	•			
Daily post-vaccination recording of solicited symptoms (days 0–14) by parents/guardians	•	•	• (dose 3 subset*)			
Collection of stool samples ***if the child is suspected to have gastroenteritis***	•	•	•	•	•	•
Recording of solicited symptoms, non serious adverse events within 42 days after dose 1, dose 2 and dose 3 (in a subset), by investigator		•	•	• (dose 3 subset*)		

FLOW SHEET (Continued)

Age	**2 months**	**4 months**	**6 months**	**8 months**	**1 year**	***2 years***
Visit	**VISIT 1**	**VISIT 2**	**VISIT 3**	**VISIT 4 DOSE 3 SUBSET ONLY***	***END OF 1ST EFFICACY PERIOD***	***END OF 2ND EFFICACY PERIOD***
Sampling timepoint	**Pre**	**Post vacc 1**	**Post vacc 2 MO 4**	**Post vacc 3 MO 6**	**Post vacc 2 MO 10**	***Post vacc 2 MO 22***
Contact (field visit) every week	◊	◊	◊	◊	◊	◊
Return of GE diary	•	•	•	• (dose 3 subset*)	•	•
GE diary transcription		•	•	• (dose 3 subset*)	•	•
Documentation of routine EPI vaccines	•	•	•	• (dose 3 subset*)	•	•
Recording medication	•	•	•	• (dose 3 subset*)		
Reporting of Serious Adverse Events occurring throughout the study period	•	•	•	• dose 3 (subset*)	•	•
Study Conclusion					•¶	•§

#Subset for immunogenicity evaluation (N = 800)
*Subset receiving three doses of study vaccine/placebo (N = 200)
◊ is used to indicate a study procedure which does not require documentation in the individual eCRFs.

¶For subjects who participate only in the first year of efficacy follow-up
§For subjects who participate in a second year of efficacy follow-up

It is the investigator's responsibility to ensure that the intervals between visits are strictly followed. These intervals determine a subject's evaluability in the according to protocol analyses.

Intervals between study visits* for subjects included in the subset receiving 3 doses of study vaccine/placebo will be as follows (amended: 3-MAY-2002)

Interval	**Size of interval**
1 (Visit 1→Visit 2)	49 - 83 days
2 (Visit 2→Visit 3)	49 - 83 days
3 (Visit 3→Visit 4)	49 – 83 days
4 (Visit 3→ ***First efficacy follow-up visit***)	160 - 200 days
5 (First efficacy follow-up visit → Second efficacy follow-up visit)	***335–395 days***

*The date of the previous visit is the reference date.

VISIT 1

6 to 12 weeks of age

DOSE 1

Informed Consent has to be obtained prior to any study procedure

ELIGIBILITY CHECKLIST

INCLUSION CRITERIA

All subjects enrolled must satisfy the following criteria at study entry :

1. A male or female child between, and including 6 and 12 weeks (42-90 days) of age at the time of the first vaccination.
2. Free of obvious health problems as established by medical history and clinical examination before entering into the study.
3. Written informed consent obtained from the parents or guardians of the subject.
4. Born after a gestation period (between 36 and 42 weeks) or a birth weight > 2000g.

EXCLUSION CRITERIA FOR ENROLMENT

The following criteria should be checked at the time of study entry. If any apply at the time of study entry, the subject must not be included in the study :

5. Use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the study vaccine or placebo or planned use during the study period.
6. Planned administration of a vaccine (including routine pediatric vaccines) not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.
7. Planned administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
8. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth. (Topical steroids are allowed.)
9. History of diphtheria, tetanus, pertussis, Hib disease and/ or hepatitis B.
10. Previous vaccination against diphtheria, tetanus, pertussis, and/or Haemophilus influenzae type b.
11. Use of antibiotics within 7 days preceding dose 1 (Warrants deferral of vaccination pending recovery of the subject).
12. Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malformation of the GI tract or other serious medical condition as determined by the investigator.
13. Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
14. History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.
15. Acute disease at time of enrollment. (Acute disease is defined as the presence of moderate or severe illness with or without fever i.e. temperature ≥ 37.5°C as measured by an axillary thermometer or ≥ 38.0°C as measured by a rectal thermometer). A temperature greater than or equal to these cut-off warrants deferral of the vaccination pending recovery of the subject. (amended: 12-FEB-2001)
16. Gastroenteritis within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).
17. Household contact with an immunosuppressed individual or pregnant women.
18. Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
19. Previous confirmed occurrence of rotavirus gastroenteritis.

ELIMINATION CRITERIA DURING THE STUDY UP TO VISIT 4

The following criteria should be checked at visits 2 and 3. These elimination criteria should be also checked on the day of dose 3 of study vaccine/placebo in the subset of subjects who receive the third dose (at Visit 4) If any become applicable during the study, the subject will not be required to discontinue the study but may be eliminated from the according-to-protocol analysis.

1. Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
2. Use of antibiotics during the period starting from 7 days before dose 1 and 2 and ending 7 days after.
3. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
4. Administration of a vaccine not foreseen by the study protocol during the period starting from 14 days before each dose of vaccine(s) and ending 14 days after.
5. Administration of oral polio vaccine during the period starting from 2 weeks before each dose of study vaccine(s) and ending 2 weeks after.
6. Administration of immunoglobulins and/or any blood products during the study period.
7. Confirmed immunosuppressive or immunodeficient condition, including HIV.

ELIMINATION CRITERIA DURING THE STUDY FROM VISIT 4 UNTIL THE STUDY END

The following criteria should be checked at the **follow-up visit at the end of the first efficacy follow-up period and at the end of the second efficacy follow-up period as applicable**. *(amended: 3-MAY-2002)* ***(amended: 20-SEP-2002)***.

8. Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
9. Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
10. Administration of immunoglobulins and/or any blood products during the study period.
11. Confirmed immunosuppressive or immunodeficient condition, including HIV.

Contraindications to vaccination

SB Biologicals' HRV vaccine or placebo:

The following adverse events constitute absolute contraindications to further administration of human rotavirus vaccine or placebo; if any of these adverse events occur during the study, the subject must not receive additional doses of vaccine or placebo but may continue other study procedures at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event :

- Hypersensitivity reaction due to the vaccine.
- Intussusception.

The following adverse events constitute contraindications to administration of human rotavirus vaccine or placebo at a given point in time; if any one of these adverse events occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol or withdrawn at the discretion of the investigator. The subject must be followed until resolution of the event, as with any adverse event.

- Axillary/rectal temperature ≥37.5°C/38.0°C
- Gastroenteritis within 7 days preceding the study vaccine administration.

DTPw-HB+Hib vaccine:

The following adverse events constitute absolute contraindications or precautions to further administration of DTPw-HB+Hib vaccine; if any of these adverse events occurs during the study, the subject must be withdrawn and must be followed until resolution of the event, as with any adverse event :

Absolute contraindications:

- Known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B or Hib vaccines.
- Encephalopathy (not due to another identifiable cause). This is defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, and/or generalized or focal seizures that persist more than a few hours, with failure to recover within 24 hours. Even though causation by DTP-containing vaccine cannot be established, no subsequent doses of pertussis vaccine should be given.

Precautions:

- *If the following adverse events occur in temporal relation to DTPw-HB+Hib vaccine administration, the decision to administer additional doses of DTPw-HB+Hib vaccine should be carefully considered:*
- Fever ≥ 40.5°C/≥ 40.0°C (rectal/axillary temperature) within 48 hours of vaccination not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting >3 hours, occurring within 48 hours of vaccination.
- Seizures with or without fever occurring within 3 days of vaccination.

Protocol	Center	Visit	Date of visit	Subject Number
444563/006	|__|__|__|	**VISIT 1**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent Date : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

DEMOGRAPHICS

Subject initials : \|__\|__\| \|__\|__\|
First name Family name

Date of birth : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

Gender : ☐ Male
☐ Female

Race : ☐ (WH) White
☐ (BL) Black
☐ (OR) Oriental
☐ (OT) Other, please specify: _____

Height : \|__\|__\|__\| cm

Weight : \|__\|__\|__\| . \|__\| kg

Is the subject eligible for the study, according to the criteria listed hereby ?

☐ Yes
☐ No, please give the corresponding criterion number(s) : _____

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

GENERAL MEDICAL HISTORY / PHYSICAL EXAMINATION

Are you aware of any pre-existing conditions or signs and/or symptoms present in the subject prior to the start of the study ?

☐ No

☐ Yes, please check appropriate box(es) and give diagnosis

			PAST	CURRENT	DIAGNOSIS
____	10	Cutaneous	☐	☐	1 ----------
			☐	☐	2 ----------
____	5	Eyes	☐	☐	1 ----------
			☐	☐	2 ----------
____	6	Ears-nose-throat	☐	☐	1 ----------
			☐	☐	2 ----------
____	2	Cardiovascular	☐	☐	1 ----------
			☐	☐	2 ----------
____	3	Respiratory	☐	☐	1 ----------
			☐	☐	2 ----------
____	1	Gastrointestinal	☐	☐	1 ----------
			☐	☐	2 ----------
____	7	Musculoskeletal	☐	☐	1 ----------
			☐	☐	2 ----------
____	8	Neurological	☐	☐	1 ----------
			☐	☐	2 ----------
____	12	Genitourinary	☐	☐	1 ----------
			☐	☐	2 ----------
____	11	Haematology	☐	☐	1 ----------
			☐	☐	2 ----------
____	4	Allergies	☐	☐	1 ----------
			☐	☐	2 ----------
____	9	Endocrine	☐	☐	1 ----------
			☐	☐	2 ----------
____	99	Other (specify)	☐	☐	1 ----------
			☐	☐	2 ----------

Please report medication(s) as specified in the protocol and fill in the **Medication** section.

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary ☐ Rectal

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes ☐ No

STOOL SAMPLE (only for a subset)

Has a stool sample been taken at the day of or 1 day prior to vaccination ?

☐ Yes
☐ No ☐ NA

Has a stool sample been taken at day 7 ± 1 ?

☐ Yes
☐ No ☐ NA

→ *** please fill the stools collection section if any stools have been collected.**

FEEDINGS

Is the child fed with :
☐ breast milk
☐ infant formula
☐ both

Did the child :
☐ receive no food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination but not 30 minutes after vaccination ?
☐ receive food within 30 minutes after vaccination but not 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 1**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / Site Route**	**Has the study vaccine been administered according to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please specify (*)*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes ☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	Please fill the **GE Episodes** Section	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0
1
2
3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 2

4 months of age

(49 – 83 days after Visit 1)

DOSE 2

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION / VACCINATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the **Contraindications** as specified in the protocol.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 2**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 1 until visit 2 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary
☐ Rectal

LABORATORY TESTS (only for a subset)

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes
☐ No ☐ NA

STOOL SAMPLE (only for a subset)

Has a stool sample been taken at the day of or 1 day prior to vaccination ?

☐ Yes
☐ No ☐ NA

Has a stool sample been taken at day 7 ± 1 ?

☐ Yes
☐ No ☐ NA

→ *** please fill the stools collection section if any stools have been collected.**

FEEDINGS

Is the child fed with : ☐ breast milk
☐ infant formula
☐ both

Did the child :
☐ receive no food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination but not 30 minutes after vaccination ?
☐ receive food within 30 minutes after vaccination but not 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 2**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / Site Route**	**Has the study vaccine been administered according to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please specify (*)*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes ☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|_|_| |_|_|_| |_|_|_|_|	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	Please fill the **GE Episodes** Section	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0 1 2 3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 3

6 months of age

(49 – 83 days after Visit 2)

DOSE 3

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION / VACCINATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the **Contraindications** as specified in the protocol.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 3**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 2 until visit 3 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature : |__|__| . |__| °C → Route : ☐ Axillary
☐ Rectal

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes
☐ No

STOOL SAMPLE

Has a stool sample been taken at the day of or 1 day prior to vaccination ?

☐ Yes
☐ No

Has a stool sample been taken at day 7 ± 1 ?

☐ Yes
☐ No

→ *** please fill the stools collection section if any stools have been collected.**

FEEDINGS

Is the child fed with : ☐ breast milk
☐ infant formula
☐ both

Did the child :
☐ receive no food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination and within 30 minutes after vaccination ?
☐ receive food within 1 hour prior to vaccination but not 30 minutes after vaccination ?
☐ receive food within 30 minutes after vaccination but not 1 hour prior to vaccination ?

Protocol		Visit		Subject Number
444563/006		**VISIT 3**		|__|__|__|__|__|

VACCINE ADMINISTRATION

Please complete the following table

VACCINE ADMINISTRATION (only one box must be checked)	**Side / Site Route**	**Has the study vaccine been administered according to the protocol ?**
☐ **HRV Vaccine or Placebo** ☐ Replacement vial (*) ☐ Wrong vial number (*) ☐ Not administered (*)	Oral	☐ Yes ☐ No → *please check all items*

(*) Comments : _____

Regurgitation within 30 minutes after vaccination ? ☐ Yes ☐ No

N.B. : Routine concomitant vaccines (DTPw-HB + Hib) and any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section.**

POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol,

→ please fill in the **Solicited Adverse Events section,** the **Non-Serious Adverse Events section** or the **Serious Adverse Event form.**

MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions,

→ please complete the **Medication section.**

SOLICITED ADVERSE EVENTS – GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

☐ Unknown
☐ No
☐ Yes, please **check a** No/Yes **box for each symptom.** If Yes is checked, please fill in the **complete line.**

GENERAL SYMPTOMS	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Ongoing After day 14?	Date of last day of symptoms Day month year	Causality
Fever ☐ No ☐ Yes → °C: ☐ Axillary ☐ Rectal	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	__.__ ☐ not taken	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Cough/runny nose ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Irritability/ Fussiness ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Loss of appetite ☐ No ☐ Yes → Intensity:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Vomiting ☐ No ☐ Yes → Number:	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	|__|__| |__|__|__| |__|__|__|__|	☐ No ☐ Yes
Diarrhea ☐ No ☐ Yes → :Number of looser than normal stools	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	|___|	☐ No ☐ Yes→	Please fill the **GE Episodes** Section	☐ No ☐ Yes
Sample taken?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes			

Treatment for diarrhea?	☐ No ☐ Yes →	☐ Oral rehydration ☐ IV rehydration ☐ Other, please specify: _____	Hospitalisation for diarrhea ☐ No ☐ Yes

Fever: Axillary ≥ 37.5 °C
Rectal ≥ 38 °C

Intensity: 0 1 2 3

→ If any of these **adverse events** are **serious** according to protocol definition,
→ Please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**

VISIT 4

8 months of age

(49 – 83 days after Visit 3)

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the **Non-Serious Adverse Events** section or the **Serious Event (SAE)** form, as appropriate.

MEDICATION / VACCINATION

→ Please report medication as specified in the protocol and fill in the **Medication** section.

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected

Protocol		Visit	Date of visit	Subject Number
444563/006		**VISIT 4**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period starting from two weeks after dose 3 until visit 4 ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken ? ☐ Yes ☐ No

END OF 1st
EFFICACY PERIOD

1 YEAR OF AGE
(160 – 200 days after Visit 3)

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

SERIOUS ADVERSE EVENTS

→ Please report serious adverse events as specified in the protocol and fill in the **Serious Event (SAE)** form, as appropriate.

CONCOMITANT VACCINATION

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected

Protocol			Date of visit	Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period between Visit 4 and the end of the 1st efficacy period ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

STOOLS

COLLECTION

END OF 1st
EFFICACY PERIOD

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

STOOLS COLLECTION

STOOLS 1	STOOLS 2	STOOLS 3
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 4	**STOOLS 5**	**STOOLS 6**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 7	**STOOLS 8**	**STOOLS 9**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 10	**STOOLS 11**	**STOOLS 12**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 13	**STOOLS 14**	**STOOLS 15**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 16	**STOOLS 17**	**STOOLS 18**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

STOOLS COLLECTION (continued)

STOOLS 19	STOOLS 20	STOOLS 21
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 22	**STOOLS 23**	**STOOLS 24**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 25	**STOOLS 26**	**STOOLS 27**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 28	**STOOLS 29**	**STOOLS 30**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 31	**STOOLS 32**	**STOOLS 33**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 34	**STOOLS 35**	**STOOLS 36**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min

GASTROENTERITIS EPISODES

END OF 1st EFFICACY PERIOD

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

CONCOMITANT VACCINATION

END OF 1st EFFICACY PERIOD

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administered during the timeframe as specified in the protocol ?

☐ No

☐ Yes, please record concomitant vaccination with trade name and / or generic name, and vaccine administration date.

Trade / Generic Name	**Administration date** day month year
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	

CONCOMITANT MEDICATION

END OF 1st EFFICACY PERIOD

GlaxoSmithKline Biologicals

MEDICATION ROUTE

CODE	LABEL
EXT	External
ID	Intradermal
IH	Inhalation
IM	Intramuscular
IR	Intraarticular
IT	Intrathecal
IV	Intravenous
NA	Intranasal
OTH	Other
PE	Parenteral
PO	Oral
PR	Rectal
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
TO	Topical
UNK	Unknown
VA	Vaginal

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

MEDICATION

→Any immunosuppressants or other immune-modifying drugs or treatments administered at ANY time during the period starting 30 days prior to the first dose of study vaccine and ending at Visit 4 must be recorded with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment. Any antibiotics administered within 7 days preceding each study vaccine/placebo administration and during the first 7 days after each study vaccine/placebo administration and any antipyretics administered at ANY time during the period starting 30 days prior to the first dose of study vaccine and ending one month (minimum 30 days) after the last dose of study vaccine/placebo must be recorded with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment.

→Any other concomitant medication administered prophylactically in anticipation of reaction to the vaccination must also be recorded with trade name and/or generic name of the medication, total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'

Have any of the above mentioned medications/treatments been administered during study period?

☐ No
☐ Yes, please complete the following table.

Trade / Generic Name	Medical Indication	Total daily dose	Route	Start and end date or check box if continuing at end of study day month year	
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					
	☐ Prophylactic			Start: |__|__| |__|__|__| |__|__|__|__| End: |__|__| |__|__|__| |__|__|__|__|	☐
For GSK					

NON-SERIOUS ADVERSE EVENTS

END OF 1st EFFICACY PERIOD

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS

(Please report all **serious adverse events** only on the **Serious Adverse Event (SAE)** form).

Have any **non-serious adverse events** occurred within **42 days** post-vaccination, excluding those recorded on the **Solicited Adverse Events** pages ?

☐ No
☐ Yes, please complete the following table.

AE No.	**AE.1**	**AE.2**	**AE.3**
Description	----------	----------	----------
	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)
For GSK			
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3
Causality In your opinion, did the vaccine possibly contribute to this AE ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Outcome	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**		|__|__|__|__|__|

NON-SERIOUS ADVERSE EVENTS (continued)

.

AE No.	**AE.4**	**AE.5**	**AE.6**
Description	----------	----------	----------
	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)	☐ Local (administration sites) ☐ General (non administration site)
For GSK			
Date Started	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol	|__|__| |__|__|__| |__|__|__|__| day month year ☐ during immediate post-vaccination period specified in protocol
Date Stopped	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__| |__|__|__| |__|__|__|__| day month year
Intensity	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3	☐ 1 ☐ 2 ☐ 3
Causality In your opinion, did the vaccine possibly contribute to this AE ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
Outcome	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown	☐ 1 Recovered ☐ 2 Recovered with sequelae ☐ 3 Ongoing at subject study conclusion ☐ 4 Died ☐ 5 Unknown

SERIOUS ADVERSE EVENT

END OF 1st EFFICACY PERIOD

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EVENT (SAE)

SAE's MUST BE REPORTED TO GLAXOSMITHKLINE BIOLOGICALS WITHIN 24 HOURS

1. **COMPLETE THE SAE PAGES OPPOSITE.**
   Please complete these pages as fully and accurately as possible in order to minimize the time you spend dealing with data queries.

   If the SAE is still ongoing at the time of reporting, please leave "Outcome" blank and update it later.

2. **PLEASE ENSURE THAT ALL INFORMATION ON THE SAE PAGES IS CONSISTENT WITH THE FOLLOWING OTHER CRF PAGES.**
   - Demographics
   - General Medical History / Physical Examination
   - Vaccine Administration page(s) (for doses administered)
   - Medication
   - Concomitant Vaccination

3. **SIGN AND DATE THE SAE PAGES 2 (AND 3). COMPLETE PAGE 3 OF THE SAE FORM IF NEEDED <u>ONLY</u>.**

4. **PHOTOCOPY THE SAE PAGES (DO NOT SEPARATE THE NCR PAGES) AND FAX THE COPY OF THE SAE PAGES TO:**
   → The study contact
   (see Investigator Site File for appropriate fax number).

   → If no photocopier <u>OR</u> fax is available, please telephone the study contact.

5. **FOR ADDITIONAL INFORMATION, PLEASE CHECK THE "ADDITIONAL INFO" BOX AND FOLLOW THE PROCEDURE EXPLAINED AT POINT 4.**

Protocol	Center	Country	GSK Receipt Date	Subject Number
444563/006	|__|__|__|		|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

SERIOUS ADVERSE EVENT (SAE)

END OF 1st EFFICACY PERIOD

☐ **(1)** Initial report ☐ **(3)** Additional info
☐ **(2)** Additional info ☐ **(4)** Additional info

Subject Demography (1)

Initials: \|__\|__\| \|__\|__\|
First name Family name

Date of birth: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

Gender : ☐ Male ☐ Female

Adverse Event *(please print clearly)* (2)

Diagnosis (or signs and symptoms if not known)

_____

_____

_____

For GSK

Date and time started : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\| (3)
(Adverse event first symptoms) day month year hours min

Date and time stopped : \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\| (4)
(If ongoing please leave blank) day month year hours min

Intensity : (5)
(maximum)
☐ 1
☐ 2
☐ 3

In your opinion, did the vaccine possibly contribute to the SAE : (6)
☐ No
☐ Yes

Outcome : (7)
(maximum)
☐ 1 Recovered
☐ 2 Recovered with sequelae
☐ 3 Ongoing
☐ 4 Died

Action taken with respect to Study Vaccine (8)
☐ None
☐ Vaccination course postponed
☐ Vaccination course stopped

Events after further vaccination (9)
☐ Event reappeared
☐ Event did not reappear
☐ Unknown at this time
☐ Not applicable

♦ **Specify criteria for considering this as a Serious Adverse Event.** (10)
(mark all that apply).

1 ☐ Result in death
→ Autopsy ? ☐ No ☐ Yes
↓
Send autopsy report when available

2 ☐ Life threatening

3 ☐ Result in persistent or significant disability/incapacity

4 ☐ Requires in-patient hospitalization.
Admission date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

5 ☐ Prolongation of existing hospitalization
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

6 ☐ Congenital anomaly / birth defect in the offspring of a study subject.

7 ☐ "Medically important" event- specify: _____

♦ **Other events (not SAE) to be reported in the same way:**
☐ Cancer

Other possible contributors: (11)
(mark all that apply)
☐ Medical history *(record in section 15)*
☐ Other medication *(record in section 14)*
☐ Protocol required procedure
☐ Other procedure
☐ Lack of efficacy
☐ Erroneous administration
☐ Other, specify : _____

(record additional information in section 19)

Was subject withdrawn due to this specific SAE ? (12)
☐ No
☐ Yes

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**	**SAE (continued)**	|__|__|__|__|__|

Study vaccine Information **(13)**

Vaccine *(specify mixed or separate)*	Dose No	Lot No	Route / Site	Date
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|

Concomitant medication / vaccination that could have contributed to this SAE **(14)**

Drug / vaccine	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Relevant intercurrent illness & medical history that could have contributed to this SAE **(15)**
(Including allergies)

Condition :	Still present? : No ☐ Yes ☐
Condition :	Still present? : No ☐ Yes ☐

Drug(s) used to treat this SAE **(16)**

Drug	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Surgical treatment for this SAE *(please specify)* **(17)**

Description *(provide a brief narrative description of the SAE including relevant diagnostic findings, lab data & evolution of the events etc…)* **(18)**

Investigator signature Date :	(1) |__|__| |__|__|__| |__|__|__|__| day month year	(2) |__|__| |__|__|__| |__|__|__|__| day month year	(3) |__|__| |__|__|__| |__|__|__|__| day month year	(4) |__|__| |__|__|__| |__|__|__|__| day month year
Please PRINT name:				

For GSK Rixensart	*Signature*	*Please PRINT name*	*Date*
Clinical Development Manager:			|__|__| |__|__|__| |__|__|__|__| day month year

AEGIS Number : \|__\|__\|__\|__\|__\|__\|__\|__\|__\|__\| . \|__\|__\|

Protocol				Subject Number
444563/006		**END OF 1st EFFICACY PERIOD**	**SAE (continued)**	|__|__|__|__|__|

Comments *(provide further comments concerning the case)* **(19)**

Investigator signature Date :	(1) |_|_| |_|_|_|_| |_|_|_|_| day month year	(2) |_|_| |_|_|_|_| |_|_|_|_| day month year	(3) |_|_| |_|_|_|_| |_|_|_|_| day month year	(4) |_|_| |_|_|_|_| |_|_|_|_| day month year
Please PRINT name:				

For GSK Rixensart	*Signature*	*Please PRINT name*	*Date*
Clinical Development Manager:			|_|_| |_|_|_|_| |_|_|_|_| day month year

AEGIS Number : |_|_|_|_|_|_|_|_|_|_| · |_|_|

STUDY

CONCLUSION

END OF 1st
EFFICACY PERIOD

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STUDY CONCLUSION AT THE END OF THE 1st EFFICACY FU PERIOD

Has the code been broken?

☐ No
☐ Yes

Did any elimination criteria become applicable during the study?

☐ No
☐ Yes, please specify: _____

Has the subject dropped out of the study?
(a drop out is a subject who did not come back for the concluding visit foreseen in the protocol.)

☐ No
☐ Yes, please mark the **ONE most appropriate** category for drop out.

- ☐ (SAE) Serious adverse event (complete the **Serious Adverse Event form**).
- ☐ (AEX) Non-Serious adverse event (complete the **Non-serious Adverse Event form**).

  please specify AE N°: _____
- ☐ (PTV) Protocol violation, please specify : _____
- ☐ (CWS) Consent withdrawal, not due to an adverse event.
- ☐ (MIG) Migrated / moved from the study area
- ☐ (LFU) Lost to follow-up.
- ☐ (OTH) Other, please specify : _____

Date of last contact : |__|__| |__|__|__| |__|__|__|__|
day month year

Was the subject in good condition at date of last contact?

☐ No, please give details within the **Adverse Events section.**
☐ Yes

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this case report form, the Non-Serious Adverse Events and Serious Adverse Event sections including any laboratory data (if appropriate) and that all information is complete and accurate.

Date : |__|__| |__|__|__| |__|__|__|__|
day month year

Investigator signature :

END OF 2nd

EFFICACY PERIOD

2 YEARS OF AGE

(335 – 395 days after end of 1st efficacy follow-up visit)

REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

GASTROENTERITIS

→ Please report **Gastroenteritis** as specified in the protocol and fill the **Gastroenteritis** episode section.

PHYSICAL EXAMINATION

→ Please perform a history – directed physical examination and report any change in current status on the **Adverse Event** page.

SERIOUS ADVERSE EVENTS

→ Please report serious adverse events as specified in the protocol and fill in the **Serious Event (SAE)** form, as appropriate.

CONCOMITANT VACCINATION

→ Please report concomitant vaccination in the **Concomitant Vaccination** section.

STOOLS COLLECTION

→ Please fill the stools collection section if any stools have been collected

Protocol			Date of visit	Subject Number
444563/006		**END OF 2nd EFFICACY PERIOD**	|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|

Height : |__|__|__| cm Weight : |__|__|__| . |__| kg

GASTROENTERITIS EPISODES

Did the subject present gastroenteritis during the period between the end of the 1st efficacy period and end of the 2nd efficacy period ?

☐ No
☐ Yes, If yes → please specify the number of episodes : |__|__|
please fill the gastroenteritis and the stools collection sections

STOOLS COLLECTION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STOOLS COLLECTION

STOOLS 1	STOOLS 2	STOOLS 3
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 4	**STOOLS 5**	**STOOLS 6**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 7	**STOOLS 8**	**STOOLS 9**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 10	**STOOLS 11**	**STOOLS 12**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 13	**STOOLS 14**	**STOOLS 15**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min
STOOLS 16	**STOOLS 17**	**STOOLS 18**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min	**Time :** |__|__|: |__|__| hour min

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STOOLS COLLECTION (continued)

STOOLS 19	STOOLS 20	STOOLS 21
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 22	**STOOLS 23**	**STOOLS 24**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 25	**STOOLS 26**	**STOOLS 27**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 28	**STOOLS 29**	**STOOLS 30**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 31	**STOOLS 32**	**STOOLS 33**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min
STOOLS 34	**STOOLS 35**	**STOOLS 36**
Date : |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year	**Date :** |__|__| |__|__|__| |__|__|__|__| day month year
Time : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min	**Time** : |__|__|: |__|__| hour min

GASTROENTERITIS EPISODES

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

Protocol				Subject Number
444563/006				|__|__|__|__|__|

GASTROENTERITIS EPISODE

EPISODE N° : |__|__|

Treatment : ☐ No
☐ Yes → If yes : ☐ Oral rehydration
☐ IV rehydration
☐ other, please specify : _____

Dehydration : ☐ No
☐ Yes → If yes : ☐ 1 – 5 %
OR ☐ ≥ 6 %

Hospitalisation : ☐ No
☐ Yes

Date day month year	**Number of looser than normal stools per day**	**Number of vomiting per day**	**Temperature (°C)** ☐ Axillary ☐ Rectal		**Sample taken**
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes
|__|__| |__|__|__| |__|__|__|__|	|__|	|__|	|__|__|__| . |__|	☐ not taken	☐ No ☐ Yes

Fever : Axillary ≥ 37.5°C
Rectal ≥ 38°C

CONCOMITANT VACCINATION

Protocol				Subject Number
444563/006				|__|__|__|__|__|

CONCOMITANT VACCINATION

Has any vaccine other than the study vaccine(s) been administered between the end of the 1st efficacy period and the end of the 2nd efficacy period ?

☐ No
☐ Yes, please record concomitant vaccination with trade name and / or generic name, and vaccine administration date.

Trade / Generic Name	**Administration date** day month year
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	
	|__|__| |__|__|__| |__|__|__|__|
For GSK	

SERIOUS ADVERSE EVENT

INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EVENT (SAE)

SAE's MUST BE REPORTED TO GLAXOSMITHKLINE BIOLOGICALS WITHIN 24 HOURS

1. **COMPLETE THE SAE PAGES OPPOSITE.**
   Please complete these pages as fully and accurately as possible in order to minimize the time you spend dealing with data queries.

   If the SAE is still ongoing at the time of reporting, please leave "Outcome" blank and update it later.

2. **PLEASE ENSURE THAT ALL INFORMATION ON THE SAE PAGES IS CONSISTENT WITH THE FOLLOWING OTHER CRF PAGES.**
   - Demographics
   - General Medical History / Physical Examination
   - Vaccine Administration page(s) (for doses administered)
   - Medication
   - Concomitant Vaccination

3. **SIGN AND DATE THE SAE PAGES 2 (AND 3). COMPLETE PAGE 3 OF THE SAE FORM IF NEEDED <u>ONLY</u>.**

4. **PHOTOCOPY THE SAE PAGES (DO NOT SEPARATE THE NCR PAGES) AND FAX THE COPY OF THE SAE PAGES TO:**
   → The study contact
   (see Investigator Site File for appropriate fax number).

   → If no photocopier <u>OR</u> fax is available, please telephone the study contact.

5. **FOR ADDITIONAL INFORMATION, PLEASE CHECK THE "ADDITIONAL INFO" BOX AND FOLLOW THE PROCEDURE EXPLAINED AT POINT 4.**

Protocol	Center	Country	GSK Receipt Date	Subject Number
444563/006	|__|__|__|		|__|__| |__|__|__| |__|__|__|__| day month year	|__|__|__|__|__|__|

SERIOUS ADVERSE EVENT (SAE)

☐ **(1)** Initial report ☐ **(3)** Additional info
☐ **(2)** Additional info ☐ **(4)** Additional info

Subject Demography (1)

Initials: \|__\|__\| \|__\|__\|
First name Family name

Date of birth: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

Gender : ☐ Male ☐ Female

Adverse Event *(please print clearly)* (2)

Diagnosis (or signs and symptoms if not known)

_____

_____

_____

For GSK

Date and time started : (3)
(Adverse event first symptoms) \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\|
day month year hours min

Date and time stopped : (4)
(If ongoing please leave blank) \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\| \|__\|__\|:\|__\|__\|
day month year hours min

Intensity : (5)
(maximum)
☐ 1
☐ 2
☐ 3

In your opinion, did the vaccine possibly contribute to the SAE : (6)
☐ No
☐ Yes

Outcome : (7)
(maximum)
☐ 1 Recovered
☐ 2 Recovered with sequelae
☐ 3 Ongoing
☐ 4 Died

Action taken with respect to Study Vaccine (8)
☐ None
☐ Vaccination course postponed
☐ Vaccination course stopped

Events after further vaccination (9)
☐ Event reappeared
☐ Event did not reappear
☐ Unknown at this time
☐ Not applicable

♦ **Specify criteria for considering this as a Serious Adverse Event.** (10)
(mark all that apply).

1 ☐ Result in death
→ Autopsy ? ☐ No ☐ Yes
↓
Send autopsy report when available

2 ☐ Life threatening

3 ☐ Result in persistent or significant disability/incapacity

4 ☐ Requires in-patient hospitalization.
Admission date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

5 ☐ Prolongation of existing hospitalization
Discharge date: \|__\|__\| \|__\|__\|__\| \|__\|__\|__\|__\|
day month year

6 ☐ Congenital anomaly / birth defect in the offspring of a study subject.

7 ☐ "Medically important" event- specify: _____

♦ **Other events (not SAE) to be reported in the same way:**
☐ Cancer

Other possible contributors: (11)
(mark all that apply)
☐ Medical history *(record in section 15)*
☐ Other medication *(record in section 14)*
☐ Protocol required procedure
☐ Other procedure
☐ Lack of efficacy
☐ Erroneous administration
☐ Other, specify : _____

(record additional information in section 19)

Was subject withdrawn due to this specific SAE ? (12)
☐ No
☐ Yes

Protocol				Subject Number
444563/006			**SAE (continued)**	|__|__|__|__|__|

Study vaccine Information **(13)**

Vaccine *(specify mixed or separate)*	Dose No	Lot No	Route / Site	Date
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|

Concomitant medication / vaccination that could have contributed to this SAE **(14)**

Drug / vaccine	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Relevant intercurrent illness & medical history that could have contributed to this SAE **(15)**
(Including allergies)

Condition :	Still present? : No ☐ Yes ☐
Condition :	Still present? : No ☐ Yes ☐

Drug(s) used to treat this SAE **(16)**

Drug	Dosage	Frequency	Route	Start date	End date
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
				|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|

Surgical treatment for this SAE *(please specify)* **(17)**

Description *(provide a brief narrative description of the SAE including relevant diagnostic findings, lab data & evolution of the events etc…)* **(18)**

Investigator signature Date :	(1) |__|__| |__|__|__| |__|__|__|__| day month year	(2) |__|__| |__|__|__| |__|__|__|__| day month year	(3) |__|__| |__|__|__| |__|__|__|__| day month year	(4) |__|__| |__|__|__| |__|__|__|__| day month year
Please PRINT name:				

For GSK Rixensart	*Signature*	*Please PRINT name*	*Date*
Clinical Development Manager:			|__|__| |__|__|__| |__|__|__|__| day month year

AEGIS Number : \|__\|__\|__\|__\|__\|__\|__\|__\|__\|__\| . \|__\|__\|

Protocol				Subject Number
444563/006			**SAE (continued)**	|__|__|__|__|__|

Comments *(provide further comments concerning the case)* **(19)**

Investigator signature Date :	(1) |_|_| |_|_|_|_| |_|_|_|_| day month year	(2) |_|_| |_|_|_|_| |_|_|_|_| day month year	(3) |_|_| |_|_|_|_| |_|_|_|_| day month year	(4) |_|_| |_|_|_|_| |_|_|_|_| day month year
Please PRINT name:				

For GSK Rixensart	*Signature*	*Please PRINT name*	*Date*
Clinical Development Manager:			|_|_| |_|_|_|_| |_|_|_|_| day month year

AEGIS Number : |_|_|_|_|_|_|_|_|_|_| · |_|_|

STUDY

CONCLUSION

AT THE END OF THE 2nd EFFICACY FU PERIOD

Protocol				Subject Number
444563/006				|__|__|__|__|__|

STUDY CONCLUSION AT THE END OF THE 2nd EFFICACY FU PERIOD

Has the code been broken?

☐ No
☐ Yes

Did any elimination criteria become applicable during the study?

☐ No
☐ Yes, please specify: _____

Has the subject dropped out of the study?
(a drop out is a subject who did not come back for the concluding visit foreseen in the protocol.)

☐ No
☐ Yes, please mark the **ONE most appropriate** category for drop out.

- ☐ (SAE) Serious adverse event (complete the **Serious Adverse Event form**).
- ☐ (AEX) Non-Serious adverse event (complete the **Non-serious Adverse Event form**).

  please specify AE N°: _____
- ☐ (PTV) Protocol violation, please specify : _____
- ☐ (CWS) Consent withdrawal, not due to an adverse event.
- ☐ (MIG) Migrated / moved from the study area
- ☐ (LFU) Lost to follow-up.
- ☐ (OTH) Other, please specify : _____

Date of last contact : |__|__| |__|__|__| |__|__|__|__|
day month year

Was the subject in good condition at date of last contact?

☐ No, please give details within the **Adverse Events section.**
☐ Yes

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this case report form, the Non-Serious Adverse Events and Serious Adverse Event sections including any laboratory data (if appropriate) and that all information is complete and accurate.

Date : |__|__| |__|__|__| |__|__|__|__|
day month year

Investigator signature :

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	**SOLICITED SYMPTOMS**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose
- **0**: Normal
- **1**: Cough/runny nose which is easily tolerated
- **2**: Cough/runny nose which interferes with daily activity
- **3**: Cough/runny nose which prevents daily activity

Irritability / fussiness:
- **0**: Behavior as usual
- **1**: Crying more than usual / no effect on normal activity
- **2**: Crying more than usual / interferes with normal activity
- **3**: Crying that cannot be comforted/ prevents normal activity

Loss of appetite:
- 0: Normal
- 1: Eating less than usual / no effect on normal activity
- 2: Eating less than usual / interferes with normal activity
- 3: Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given.

SOLICITED SYMPTOMS	Day 0	Day 1 evening	Day 2 evening	Day 3 evening	Day 4 evening	Day 5 evening	Day 6 evening	Day 7 evening	Day 8 evening	Day 9 evening	Day 10 evening	Day 11 evening	Day 12 evening	Day 13 evening	Day 14 evening	Ongoing after day 14?	Date of last day of symptoms day month year
Date:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____		
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Irritability/fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	**if ongoing after day 14, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET**
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

MEDICATION FOR DIARRHEA
- ☐ None
- ☐ Oral rehydration
- ☐ Other, please specify----------

HOSPITALISATION FOR DIARRHEA :
- ☐ No
- ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__||__|__|__||__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 14**	**DOSE 1**	|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea.

SOLICITED GASTROENTERITIS SYMPTOMS	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__| |__|__|__| |__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	GASTROENTERITIS EPISODES		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS is defined as presence of diarrhea
DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

Protocol	DIARY CARD	DOSE 1	Subject number
444563/006 (Rota-006)	**OTHER GENERAL SYMPTOMS AND MEDICATION**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

INTENSITY:

Other general symptoms:

1: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse event which prevents normal, everyday activities. (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten / a day-care center and would cause the parents / guardians to seek medical advice).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis symptoms) Please give details below	Intensity	Start date day month year	End date or check box if continuing day month year	
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

MEDICATION Please fill in below if any medication has been taken since the vaccination **(excluding oral rehydration)**		Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
Trade / generic name	Reason				
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**SOLICITED SYMPTOMS**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose
- **0**: Normal
- **1**: Cough/runny nose which is easily tolerated
- **2**: Cough/runny nose which interferes with daily activity
- **3**: Cough/runny nose which prevents daily activity

Irritability / fussiness:
- **0**: Behavior as usual
- **1**: Crying more than usual / no effect on normal activity
- **2**: Crying more than usual / interferes with normal activity
- **3**: Crying that cannot be comforted/ prevents normal activity

Loss of appetite:
- 0: Normal
- 1: Eating less than usual / no effect on normal activity
- 2: Eating less than usual / interferes with normal activity
- 3: Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given.

SOLICITED SYMPTOMS	Day 0	Day 1 evening	Day 2 evening	Day 3 evening	Day 4 evening	Day 5 evening	Day 6 evening	Day 7 evening	Day 8 evening	Day 9 evening	Day 10 evening	Day 11 evening	Day 12 evening	Day 13 evening	Day 14 evening	Ongoing after day 14?	Date of last day of symptoms day month year
Date:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____		
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|
Irritability/fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__|__|__|__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	**if ongoing after day 14, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET**
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

MEDICATION FOR DIARRHEA
- ☐ None
- ☐ Oral rehydration
- ☐ Other, please specify----------

HOSPITALISATION FOR DIARRHEA :
- ☐ No
- ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__|/|__|__|__|/|__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 14**	**DOSE 2**	|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea.

SOLICITED GASTROENTERITIS SYMPTOMS	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__| |__|__|__| |__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**GASTROENTERITIS EPISODES**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS is defined as presence of diarrhea.
DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episode of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and/or vomiting and record whether medical treatment was given

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

Protocol	DIARY CARD	DOSE 2	Subject number
444563/006 (Rota-006)	**OTHER GENERAL SYMPTOMS AND MEDICATION**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

INTENSITY:

Other general symptoms:

1: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse event which prevents normal, everyday activities. (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten / a day-care center and would cause the parents / guardians to seek medical advice).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis symptoms) Please give details below	Intensity	Start date day month year	End date or check box if continuing day month year	
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

MEDICATION Please fill in below if any medication has been taken since the vaccination **(excluding oral rehydration)**		Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
Trade / generic name	Reason				
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

Protocol	DIARY CARD	DOSE 3	Subject number
444563/006 (Rota-006)	**SOLICITED SYMPTOMS**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

INTENSITY:

Cough/runny nose
- **0**: Normal
- **1**: Cough/runny nose which is easily tolerated
- **2**: Cough/runny nose which interferes with daily activity
- **3**: Cough/runny nose which prevents daily activity

Irritability / fussiness:
- **0**: Behavior as usual
- **1**: Crying more than usual / no effect on normal activity
- **2**: Crying more than usual / interferes with normal activity
- **3**: Crying that cannot be comforted/ prevents normal activity

Loss of appetite:
- 0: Normal
- 1: Eating less than usual / no effect on normal activity
- 2: Eating less than usual / interferes with normal activity
- 3: Not eating at all

DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given.

SOLICITED SYMPTOMS	Day 0	Day 1 evening	Day 2 evening	Day 3 evening	Day 4 evening	Day 5 evening	Day 6 evening	Day 7 evening	Day 8 evening	Day 9 evening	Day 10 evening	Day 11 evening	Day 12 evening	Day 13 evening	Day 14 evening	Ongoing after day 14?	Date of last day of symptoms day month year
Date:	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____	_____		
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Cough/runny nose → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Irritability/fussiness → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Loss of appetite → intensity:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	|__|__||__|__|__||__|__|__|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	☐ No ☐ Yes →	**if ongoing after day 14, please complete the FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOM SHEET**
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes		

MEDICATION FOR DIARRHEA
- ☐ None
- ☐ Oral rehydration
- ☐ Other, please specify----------

HOSPITALISATION FOR DIARRHEA :
- ☐ No
- ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__||__|__|__||__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD		Subject number
444563/006 (Rota-006)	**FOLLOW-UP OF SOLICITED DIARRHEA SYMPTOMS ONGOING AFTER DAY 14**	**DOSE 3**	|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

DIARRHEA is defined as three or more looser than normal stools within a day.

VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea.

SOLICITED GASTROENTERITIS SYMPTOMS	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____	**Date** _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

PLEASE DO NOT FORGET TO BRING BACK THE DIARY CARD ON |__|__| |__|__|__| |__|__|__|__| -

IN CASE OF HOSPITALIZATION, PLEASE INFORM: ..... ☎: .....

Protocol	DIARY CARD	DOSE 3	Subject number
444563/006 (Rota-006)	GASTROENTERITIS EPISODES		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

Temperature: Please record the temperature every day. If temperature has been taken more than once a day, please report the highest value for the day.

GASTROENTERITIS is defined as presence of diarrhea
DIARRHEA is defined as three or more looser than normal stools within a day.
VOMITING is defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

(*) Please collect stools samples in case of diarrhea and record whether medical treatment was given

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

EPISODE N°: _____

GASTROENTERITIS SYMPTOMS	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____	Date _____
Temperature → °C: ☐ Axillary ☐ Rectal	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__	__.__
Vomiting → number :	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Diarrhea (*) → number of looser than normal stools:	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|	|__|
Stools samples taken ?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes

Medication for gastroenteritis episode
☐ None
☐ Oral rehydration
☐ Other, please specify:
_____
_____
_____

Hospitalisation for gastroenteritis episode
☐ No
☐ Yes

Protocol	DIARY CARD	DOSE 3	Subject number
444563/006 (Rota-006)	**OTHER GENERAL SYMPTOMS AND MEDICATION**		|__|__|__|__|__|

Please fill in below and assess the occurrence of any of the following signs or symptoms according to the criteria listed hereafter:

INTENSITY:

Other general symptoms:

1: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse event which prevents normal, everyday activities. (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten / a day-care center and would cause the parents / guardians to seek medical advice).

OTHER GENERAL SYMPTOMS (excluding gastroenteritis symptoms) Please give details below	Intensity	Start date day month year	End date or check box if continuing day month year	
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
	|__|	|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

MEDICATION Please fill in below if any medication has been taken since the vaccination **(excluding oral rehydration)**		Total Daily Dose	Start date day month year	End date or check box if continuing day month year	
Trade / generic name	Reason				
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐
			|__|__|__|__|__|__|__|__|	|__|__|__|__|__|__|__|__|	☐

GlaxoSmithKline

Investigator CV

This section contained Principal Investigator's Curriculum Vitae and has been excluded to protect Principal Investigator privacy.

Randomisation List

Subjects from Group 1 : HRV10E4.7ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	1	[redacted]	21
	1		21
	2		22
	2		22
	3		23
	3		23
	4		24
	4		24
	5		25
	5		25
	6		26
	6		26
	7		27
	7		27
	8		28
	8		28
	9		29
	9		29
	10		30
	10		30
	11		31
	11		31
	12		32
	12		32
	13		33
	13		33
	14		34
	14		34
	15		35
	15		35
	16		36
	16		36
	17		37
	17		37
	18		38
	18		38
	19		39
	19		39
	20		40
	20		40

Subjects from Group 1 : HRV10E4.7ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	41	[redacted]	61
	41		61
	42		62
	42		62
	43		63
	43		63
	44		64
	44		64
	45		65
	45		65
	46		66
	46		66
	47		67
	47		67
	48		68
	48		68
	49		69
	49		69
	50		70
	50		70
	51		71
	51		71
	52		72
	52		72
	53		73
	53		73
	54		74
	54		74
	55		75
	55		75
	56		76
	56		76
	57		77
	57		77
	58		78
	58		78
	59		79
	59		79
	60		80
	60		80

Subjects from Group 1 : HRV10E4.7ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	81	[redacted]	101
	81		101
	82		102
	82		102
	83		103
	83		103
	84		104
	84		104
	85		105
	85		105
	86		106
	86		106
	87		107
	87		107
	88		108
	88		108
	89		109
	89		109
	90		110
	90		110
	91		111
	91		111
	92		112
	92		112
	93		113
	93		113
	94		114
	94		114
	95		115
	95		115
	96		116
	96		116
	97		117
	97		117
	98		118
	98		118
	99		119
	99		119
	100		120
	100		120

Subjects from Group 1 : HRV10E4.7ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	121	[redacted]	141
[redacted]	121	[redacted]	141
[redacted]	122	[redacted]	142
[redacted]	122	[redacted]	142
[redacted]	123	[redacted]	143
[redacted]	123	[redacted]	143
[redacted]	124	[redacted]	144
[redacted]	124	[redacted]	144
[redacted]	125	[redacted]	145
[redacted]	125	[redacted]	145
[redacted]	126	[redacted]	146
[redacted]	126	[redacted]	146
[redacted]	127	[redacted]	147
[redacted]	127	[redacted]	147
[redacted]	128	[redacted]	148
[redacted]	128	[redacted]	148
[redacted]	129	[redacted]	149
[redacted]	129	[redacted]	149
[redacted]	130	[redacted]	150
[redacted]	130	[redacted]	150
[redacted]	131	[redacted]	151
[redacted]	131	[redacted]	151
[redacted]	132	[redacted]	152
[redacted]	132	[redacted]	152
[redacted]	133	[redacted]	153
[redacted]	133	[redacted]	153
[redacted]	134	[redacted]	154
[redacted]	134	[redacted]	154
[redacted]	135	[redacted]	155
[redacted]	135	[redacted]	155
[redacted]	136	[redacted]	156
[redacted]	136	[redacted]	156
[redacted]	137	[redacted]	157
[redacted]	137	[redacted]	157
[redacted]	138	[redacted]	158
[redacted]	138	[redacted]	158
[redacted]	139	[redacted]	159
[redacted]	139	[redacted]	159
[redacted]	140	[redacted]	160
[redacted]	140	[redacted]	160

Subjects from Group 1 : HRV10E4.7ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	161	[redacted]	181
[redacted]	161	[redacted]	181
[redacted]	162	[redacted]	182
[redacted]	162	[redacted]	182
[redacted]	163	[redacted]	207
[redacted]	163	[redacted]	207
[redacted]	164	[redacted]	208
[redacted]	164	[redacted]	208
[redacted]	165	[redacted]	209
[redacted]	165	[redacted]	209
[redacted]	166	[redacted]	210
[redacted]	166	[redacted]	210
[redacted]	167	[redacted]	211
[redacted]	167	[redacted]	211
[redacted]	168	[redacted]	212
[redacted]	168	[redacted]	212
[redacted]	169	[redacted]	213
[redacted]	169	[redacted]	213
[redacted]	170	[redacted]	214
[redacted]	170	[redacted]	214
[redacted]	171	[redacted]	215
[redacted]	171	[redacted]	215
[redacted]	172	[redacted]	216
[redacted]	172	[redacted]	216
[redacted]	173	[redacted]	217
[redacted]	173	[redacted]	217
[redacted]	174	[redacted]	218
[redacted]	174	[redacted]	218
[redacted]	175	[redacted]	219
[redacted]	175	[redacted]	219
[redacted]	176	[redacted]	220
[redacted]	176	[redacted]	220
[redacted]	177	[redacted]	221
[redacted]	177	[redacted]	221
[redacted]	178	[redacted]	222
[redacted]	178	[redacted]	222
[redacted]	179	[redacted]	223
[redacted]	179	[redacted]	223
[redacted]	180	[redacted]	224
[redacted]	180	[redacted]	224

Subjects from Group 1 : HRV10E4.7ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	225	[redacted]	311
[redacted]	225	[redacted]	311
[redacted]	226	[redacted]	312
[redacted]	226	[redacted]	312
[redacted]	227	[redacted]	313
[redacted]	227	[redacted]	313
[redacted]	228	[redacted]	314
[redacted]	228	[redacted]	314
[redacted]	229	[redacted]	315
[redacted]	229	[redacted]	315
[redacted]	230	[redacted]	316
[redacted]	231	[redacted]	316
[redacted]	231	[redacted]	317
[redacted]	232	[redacted]	317
[redacted]	233	[redacted]	318
[redacted]	234	[redacted]	318
[redacted]	299	[redacted]	319
[redacted]	299	[redacted]	319
[redacted]	300	[redacted]	320
[redacted]	300	[redacted]	320
[redacted]	301	[redacted]	321
[redacted]	301	[redacted]	321
[redacted]	302	[redacted]	322
[redacted]	302	[redacted]	322
[redacted]	303	[redacted]	323
[redacted]	303	[redacted]	323
[redacted]	304	[redacted]	324
[redacted]	304	[redacted]	324
[redacted]	305	[redacted]	325
[redacted]	305	[redacted]	325
[redacted]	306	[redacted]	326
[redacted]	306	[redacted]	326
[redacted]	307	[redacted]	327
[redacted]	307	[redacted]	327
[redacted]	308	[redacted]	328
[redacted]	308	[redacted]	328
[redacted]	309	[redacted]	329
[redacted]	309	[redacted]	329
[redacted]	310	[redacted]	330
[redacted]	310	[redacted]	330

Subjects from Group 1 : HRV10E4.7ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	331	[redacted]	351
[redacted]	331	[redacted]	351
[redacted]	332	[redacted]	352
[redacted]	332	[redacted]	352
[redacted]	333	[redacted]	353
[redacted]	333	[redacted]	353
[redacted]	334	[redacted]	354
[redacted]	334	[redacted]	354
[redacted]	335	[redacted]	237
[redacted]	335	[redacted]	237
[redacted]	336	[redacted]	238
[redacted]	336	[redacted]	238
[redacted]	337	[redacted]	239
[redacted]	337	[redacted]	239
[redacted]	338	[redacted]	240
[redacted]	338	[redacted]	240
[redacted]	339	[redacted]	241
[redacted]	339	[redacted]	241
[redacted]	340	[redacted]	242
[redacted]	340	[redacted]	242
[redacted]	341	[redacted]	243
[redacted]	341	[redacted]	243
[redacted]	342	[redacted]	244
[redacted]	342	[redacted]	244
[redacted]	343	[redacted]	245
[redacted]	343	[redacted]	245
[redacted]	344	[redacted]	246
[redacted]	344	[redacted]	246
[redacted]	345	[redacted]	247
[redacted]	345	[redacted]	247
[redacted]	346	[redacted]	248
[redacted]	346	[redacted]	248
[redacted]	347	[redacted]	249
[redacted]	347	[redacted]	249
[redacted]	348	[redacted]	250
[redacted]	348	[redacted]	250
[redacted]	349	[redacted]	251
[redacted]	349	[redacted]	251
[redacted]	350	[redacted]	252
[redacted]	350	[redacted]	252

Subjects from Group 1 : HRV10E4.7ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb
[redacted]	253
	253
	254
	254
	255
	255
	256
	256
	257
	257
	258
	258
	259
	259
	260
	260
	261
	261
	262
	272
	274
	275
	275
	276
	276
	277
	277
	278
	278
	279
	279
	280
	280
	281
	281
	282
	282
	283
	283
	284

Sub. No.	Bl. nb
[redacted]	284
	285
	285
	286
	286
	287
	287
	288
	288
	289
	289
	290
	290
	291
	291
	292
	292

Subjects from Group 2 : HRV placebo - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	1	[redacted]	21
	1		21
	2		22
	2		22
	3		23
	3		23
	4		24
	4		24
	5		25
	5		25
	6		26
	6		26
	7		27
	7		27
	8		28
	8		28
	9		29
	9		29
	10		30
	10		30
	11		31
	11		31
	12		32
	12		32
	13		33
	13		33
	14		34
	14		34
	15		35
	15		35
	16		36
	16		36
	17		37
	17		37
	18		38
	18		38
	19		39
	19		39
	20		40
	20		40

Subjects from Group 2 : HRV placebo - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	41	[redacted]	61
	41		61
	42		62
	42		62
	43		63
	43		63
	44		64
	44		64
	45		65
	45		65
	46		66
	46		66
	47		67
	47		67
	48		68
	48		68
	49		69
	49		69
	50		70
	50		70
	51		71
	51		71
	52		72
	52		72
	53		73
	53		73
	54		74
	54		74
	55		75
	55		75
	56		76
	56		76
	57		77
	57		77
	58		78
	58		78
	59		79
	59		79
	60		80
	60		80

Subjects from Group 2 : HRV placebo - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	81	[redacted]	101
	81		101
	82		102
	82		102
	83		103
	83		103
	84		104
	84		104
	85		105
	85		105
	86		106
	86		106
	87		107
	87		107
	88		108
	88		108
	89		109
	89		109
	90		110
	90		110
	91		111
	91		111
	92		112
	92		112
	93		113
	93		113
	94		114
	94		114
	95		115
	95		115
	96		116
	96		116
	97		117
	97		117
	98		118
	98		118
	99		119
	99		119
	100		120
	100		120

Subjects from Group 2 : HRV placebo - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	121	[redacted]	141
	121		141
	122		142
	122		142
	123		143
	123		143
	124		144
	124		144
	125		145
	125		145
	126		146
	126		146
	127		147
	127		147
	128		148
	128		148
	129		149
	129		149
	130		150
	130		150
	131		151
	131		151
	132		152
	132		152
	133		153
	133		153
	134		154
	134		154
	135		155
	135		155
	136		156
	136		156
	137		157
	137		157
	138		158
	138		158
	139		159
	139		159
	140		160
	140		160

Subjects from Group 2 : HRV placebo - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	161	[redacted]	181
	161		181
	162		182
	162		182
	163		207
	163		207
	164		208
	164		208
	165		209
	165		209
	166		210
	166		210
	167		211
	167		211
	168		212
	168		212
	169		213
	169		213
	170		214
	170		214
	171		215
	171		215
	172		216
	172		216
	173		217
	173		217
	174		218
	174		218
	175		219
	175		219
	176		220
	176		220
	177		221
	177		221
	178		222
	178		222
	179		223
	179		223
	180		224
	180		224

Subjects from Group 2 : HRV placebo - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	225	[redacted]	309
	225		310
	226		310
	227		311
	227		311
	228		312
	228		312
	229		313
	229		313
	230		314
	230		314
	231		315
	231		315
	232		316
	232		316
	233		317
	233		317
	234		318
	234		318
	299		319
	299		319
	300		320
	300		320
	301		321
	301		321
	302		322
	302		322
	303		323
	303		323
	304		324
	304		324
	305		325
	305		325
	306		326
	306		326
	307		327
	307		327
	308		328
	308		328
	309		329

Subjects from Group 2 : HRV placebo - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	329	[redacted]	349
	330		350
	330		350
	331		351
	331		351
	332		352
	332		352
	333		353
	333		353
	334		354
	334		354
	335		237
	335		237
	336		238
	336		238
	337		239
	337		239
	338		240
	338		240
	339		241
	339		241
	340		242
	340		242
	341		243
	341		243
	342		244
	342		244
	343		245
	343		245
	344		246
	344		246
	345		247
	345		247
	346		248
	346		248
	347		249
	347		249
	348		250
	348		250
	349		251

Subjects from Group 2 : HRV placebo - subjects planned to receive 2 doses

Sub. No.	Bl. nb
[redacted]	251
	252
	252
	253
	253
	254
	254
	255
	255
	256
	256
	257
	257
	258
	258
	259
	259
	260
	260
	261
	261
	274
	275
	275
	276
	276
	277
	277
	278
	278
	279
	279
	280
	280
	281
	281
	282
	282
	283
	283

Sub. No.	Bl. nb
[redacted]	284
	284
	285
	285
	286
	286
	287
	287
	288
	288
	289
	289
	290
	290
	291
	291
	292
	292

Subjects from Group 3 : HRV10E5.8ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	1	[redacted]	21
	1		21
	2		22
	2		22
	3		23
	3		23
	4		24
	4		24
	5		25
	5		25
	6		26
	6		26
	7		27
	7		27
	8		28
	8		28
	9		29
	9		29
	10		30
	10		30
	11		31
	11		31
	12		32
	12		32
	13		33
	13		33
	14		34
	14		34
	15		35
	15		35
	16		36
	16		36
	17		37
	17		37
	18		38
	18		38
	19		39
	19		39
	20		40
	20		40

Subjects from Group 3 : HRV10E5.8ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	41	[redacted]	61
	41		61
	42		62
	42		62
	43		63
	43		63
	44		64
	44		64
	45		65
	45		65
	46		66
	46		66
	47		67
	47		67
	48		68
	48		68
	49		69
	49		69
	50		70
	50		70
	51		71
	51		71
	52		72
	52		72
	53		73
	53		73
	54		74
	54		74
	55		75
	55		75
	56		76
	56		76
	57		77
	57		77
	58		78
	58		78
	59		79
	59		79
	60		80
	60		80

Subjects from Group 3 : HRV10E5.8ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	81	[redacted]	101
	81		101
	82		102
	82		102
	83		103
	83		103
	84		104
	84		104
	85		105
	85		105
	86		106
	86		106
	87		107
	87		107
	88		108
	88		108
	89		109
	89		109
	90		110
	90		110
	91		111
	91		111
	92		112
	92		112
	93		113
	93		113
	94		114
	94		114
	95		115
	95		115
	96		116
	96		116
	97		117
	97		117
	98		118
	98		118
	99		119
	99		119
	100		120
	100		120

Subjects from Group 3 : HRV10E5.8ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	121	[redacted]	141
	121		141
	122		142
	122		142
	123		143
	123		143
	124		144
	124		144
	125		145
	125		145
	126		146
	126		146
	127		147
	127		147
	128		148
	128		148
	129		149
	129		149
	130		150
	130		150
	131		151
	131		151
	132		152
	132		152
	133		153
	133		153
	134		154
	134		154
	135		155
	135		155
	136		156
	136		156
	137		157
	137		157
	138		158
	138		158
	139		159
	139		159
	140		160
	140		160

Subjects from Group 3 : HRV10E5.8ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	161	[redacted]	181
	161		181
	162		182
	162		182
	163		207
	163		207
	164		208
	164		208
	165		209
	165		209
	166		210
	166		210
	167		211
	167		211
	168		212
	168		212
	169		213
	169		213
	170		214
	170		214
	171		215
	171		215
	172		216
	172		216
	173		217
	173		217
	174		218
	174		218
	175		219
	175		219
	176		220
	176		220
	177		221
	177		221
	178		222
	178		222
	179		223
	179		223
	180		224
	180		224

Subjects from Group 3 : HRV10E5.8ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	225	[redacted]	310
	225		310
	226		311
	226		311
	227		312
	228		312
	228		313
	229		313
	229		314
	230		314
	230		315
	231		315
	231		316
	232		316
	233		317
	233		317
	234		318
	235		318
	299		319
	299		319
	300		320
	300		320
	301		321
	301		321
	302		322
	302		322
	303		323
	303		323
	304		324
	304		324
	305		325
	305		325
	306		326
	306		326
	307		327
	307		327
	308		328
	308		328
	309		329
	309		329

Subjects from Group 3 : HRV10E5.8ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	330	[redacted]	350
	330		350
	331		351
	331		351
	332		352
	332		352
	333		353
	333		353
	334		354
	334		354
	335		237
	335		237
	336		238
	336		238
	337		239
	337		239
	338		240
	338		240
	339		241
	339		241
	340		242
	340		242
	341		243
	341		243
	342		244
	342		244
	343		245
	343		245
	344		246
	344		246
	345		247
	345		247
	346		248
	346		248
	347		249
	347		249
	348		250
	348		250
	349		251
	349		251

Subjects from Group 3 : HRV10E5.8ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	252	[redacted]	284
	252		284
	253		285
	253		285
	254		286
	254		286
	255		287
	255		287
	256		288
	256		288
	257		289
	257		289
	258		290
	258		290
	259		291
	259		291
	260		292
	260		292
	261		
	261		
	274		
	274		
	275		
	275		
	276		
	276		
	277		
	277		
	278		
	278		
	279		
	279		
	280		
	280		
	281		
	281		
	282		
	282		
	283		
	283		

Subjects from Group 4 : HRV10E5.2ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	1	[redacted]	21
	1		21
	2		22
	2		22
	3		23
	3		23
	4		24
	4		24
	5		25
	5		25
	6		26
	6		26
	7		27
	7		27
	8		28
	8		28
	9		29
	9		29
	10		30
	10		30
	11		31
	11		31
	12		32
	12		32
	13		33
	13		33
	14		34
	14		34
	15		35
	15		35
	16		36
	16		36
	17		37
	17		37
	18		38
	18		38
	19		39
	19		39
	20		40
	20		40

Subjects from Group 4 : HRV10E5.2ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	41	[redacted]	61
	41		61
	42		62
	42		62
	43		63
	43		63
	44		64
	44		64
	45		65
	45		65
	46		66
	46		66
	47		67
	47		67
	48		68
	48		68
	49		69
	49		69
	50		70
	50		70
	51		71
	51		71
	52		72
	52		72
	53		73
	53		73
	54		74
	54		74
	55		75
	55		75
	56		76
	56		76
	57		77
	57		77
	58		78
	58		78
	59		79
	59		79
	60		80
	60		80

Subjects from Group 4 : HRV10E5.2ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	81	[redacted]	101
	81		101
	82		102
	82		102
	83		103
	83		103
	84		104
	84		104
	85		105
	85		105
	86		106
	86		106
	87		107
	87		107
	88		108
	88		108
	89		109
	89		109
	90		110
	90		110
	91		111
	91		111
	92		112
	92		112
	93		113
	93		113
	94		114
	94		114
	95		115
	95		115
	96		116
	96		116
	97		117
	97		117
	98		118
	98		118
	99		119
	99		119
	100		120
	100		120

Subjects from Group 4 : HRV10E5.2ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	121	[redacted]	141
	121		141
	122		142
	122		142
	123		143
	123		143
	124		144
	124		144
	125		145
	125		145
	126		146
	126		146
	127		147
	127		147
	128		148
	128		148
	129		149
	129		149
	130		150
	130		150
	131		151
	131		151
	132		152
	132		152
	133		153
	133		153
	134		154
	134		154
	135		155
	135		155
	136		156
	136		156
	137		157
	137		157
	138		158
	138		158
	139		159
	139		159
	140		160
	140		160

Subjects from Group 4 : HRV10E5.2ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	161	[redacted]	181
[redacted]	161	[redacted]	181
[redacted]	162	[redacted]	182
[redacted]	162	[redacted]	182
[redacted]	163	[redacted]	207
[redacted]	163	[redacted]	207
[redacted]	164	[redacted]	208
[redacted]	164	[redacted]	208
[redacted]	165	[redacted]	209
[redacted]	165	[redacted]	209
[redacted]	166	[redacted]	210
[redacted]	166	[redacted]	210
[redacted]	167	[redacted]	211
[redacted]	167	[redacted]	211
[redacted]	168	[redacted]	212
[redacted]	168	[redacted]	212
[redacted]	169	[redacted]	213
[redacted]	169	[redacted]	213
[redacted]	170	[redacted]	214
[redacted]	170	[redacted]	214
[redacted]	171	[redacted]	215
[redacted]	171	[redacted]	215
[redacted]	172	[redacted]	216
[redacted]	172	[redacted]	216
[redacted]	173	[redacted]	217
[redacted]	173	[redacted]	217
[redacted]	174	[redacted]	218
[redacted]	174	[redacted]	218
[redacted]	175	[redacted]	219
[redacted]	175	[redacted]	219
[redacted]	176	[redacted]	220
[redacted]	176	[redacted]	220
[redacted]	177	[redacted]	221
[redacted]	177	[redacted]	221
[redacted]	178	[redacted]	222
[redacted]	178	[redacted]	222
[redacted]	179	[redacted]	223
[redacted]	179	[redacted]	223
[redacted]	180	[redacted]	224
[redacted]	180	[redacted]	225

Subjects from Group 4 : HRV10E5.2ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	225	[redacted]	309
[redacted]	226	[redacted]	310
[redacted]	226	[redacted]	310
[redacted]	227	[redacted]	311
[redacted]	227	[redacted]	311
[redacted]	228	[redacted]	312
[redacted]	228	[redacted]	312
[redacted]	229	[redacted]	313
[redacted]	229	[redacted]	313
[redacted]	230	[redacted]	314
[redacted]	230	[redacted]	314
[redacted]	231	[redacted]	315
[redacted]	231	[redacted]	315
[redacted]	232	[redacted]	316
[redacted]	232	[redacted]	316
[redacted]	233	[redacted]	317
[redacted]	233	[redacted]	317
[redacted]	234	[redacted]	318
[redacted]	234	[redacted]	318
[redacted]	299	[redacted]	319
[redacted]	299	[redacted]	319
[redacted]	300	[redacted]	320
[redacted]	300	[redacted]	320
[redacted]	301	[redacted]	321
[redacted]	301	[redacted]	321
[redacted]	302	[redacted]	322
[redacted]	302	[redacted]	322
[redacted]	303	[redacted]	323
[redacted]	303	[redacted]	323
[redacted]	304	[redacted]	324
[redacted]	304	[redacted]	324
[redacted]	305	[redacted]	325
[redacted]	305	[redacted]	325
[redacted]	306	[redacted]	326
[redacted]	306	[redacted]	326
[redacted]	307	[redacted]	327
[redacted]	307	[redacted]	327
[redacted]	308	[redacted]	328
[redacted]	308	[redacted]	328
[redacted]	309	[redacted]	329

Subjects from Group 4 : HRV10E5.2ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	329	[redacted]	349
[redacted]	330	[redacted]	350
[redacted]	330	[redacted]	350
[redacted]	331	[redacted]	351
[redacted]	331	[redacted]	351
[redacted]	332	[redacted]	352
[redacted]	332	[redacted]	352
[redacted]	333	[redacted]	353
[redacted]	333	[redacted]	353
[redacted]	334	[redacted]	354
[redacted]	334	[redacted]	354
[redacted]	335	[redacted]	237
[redacted]	335	[redacted]	237
[redacted]	336	[redacted]	238
[redacted]	336	[redacted]	238
[redacted]	337	[redacted]	239
[redacted]	337	[redacted]	239
[redacted]	338	[redacted]	240
[redacted]	338	[redacted]	240
[redacted]	339	[redacted]	241
[redacted]	339	[redacted]	241
[redacted]	340	[redacted]	242
[redacted]	340	[redacted]	242
[redacted]	341	[redacted]	243
[redacted]	341	[redacted]	243
[redacted]	342	[redacted]	244
[redacted]	342	[redacted]	244
[redacted]	343	[redacted]	245
[redacted]	343	[redacted]	245
[redacted]	344	[redacted]	246
[redacted]	344	[redacted]	246
[redacted]	345	[redacted]	247
[redacted]	345	[redacted]	247
[redacted]	346	[redacted]	248
[redacted]	346	[redacted]	248
[redacted]	347	[redacted]	249
[redacted]	347	[redacted]	249
[redacted]	348	[redacted]	250
[redacted]	348	[redacted]	250
[redacted]	349	[redacted]	251

Subjects from Group 4 : HRV10E5.2ffu - subjects planned to receive 2 doses

Sub. No.	Bl. nb	Sub. No.	Bl. nb
[redacted]	251	[redacted]	284
	252		284
	252		285
	253		285
	253		286
	254		286
	254		287
	255		287
	255		288
	256		288
	256		289
	257		289
	257		290
	258		290
	258		291
	259		291
	259		292
	260		292
	260		
	261		
	261		
	274		
	275		
	275		
	276		
	276		
	277		
	277		
	278		
	278		
	279		
	279		
	280		
	280		
	281		
	281		
	282		
	282		
	283		
	283		

Subjects from Group 5 : HRV10E4.7ffu - subjects planned to receive 3 doses

Sub. No.	Bl. nb
[redacted]	230
	232
	233
	234
	235
	235
	236
	236
	262
	263
	263
	264
	264
	265
	265
	266
	266
	267
	267
	268
	268
	269
	269
	270
	270
	271
	271
	272
	273
	273
	274

Subjects from Group 6 : HRV placebo - subjects planned to receive 3 doses

Sub. No.	Bl. nb
[redacted]	226
	235
	235
	236
	236
	262
	262
	263
	263
	264
	264
	265
	265
	266
	266
	267
	267
	268
	268
	269
	269
	270
	270
	271
	271
	272
	272
	273
	273
	274

Subjects from Group 7 : HRV10E5.8ffu - subjects planned to receive 3 doses

Sub. No.	Bl. nb
[redacted]	227
	232
	234
	235
	236
	236
	262
	262
	263
	263
	264
	264
	265
	265
	266
	266
	267
	267
	268
	268
	269
	269
	270
	270
	271
	271
	272
	272
	273
	273

Subjects from Group 8 : HRV10E5.2ffu - subjects planned to receive 3 doses

Sub. No.	Bl. nb
[redacted]	224
	235
	235
	236
	236
	262
	262
	263
	263
	264
	264
	265
	265
	266
	266
	267
	267
	268
	268
	269
	269
	270
	270
	271
	271
	272
	272
	273
	273
	274

Publications referenced in the report

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

CONFIDENTIAL

Final Study Report for Clinical Trial 444563/004 (rota-004)

Title: A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants approximately 2 months of age and previously uninfected with HRV.

Study vaccines: GlaxoSmithKline Biologicals' live attenuated human rotavirus vaccine.

CPMS Study No.: 444563/004 (rota-004)

Indication: Two oral doses at two months interval to healthy infants, 2 months (6–12 weeks) of age at the time of Dose 1.

Principal Investigator: Prof. [redacted]

Date of First Visit: August 21, 2000

Data Lock Point: July 11, 2001

Coordinating Author: [redacted] Scientific Writer

Contributing authors: [redacted] Biometrician

[redacted] Clinical Development Manager

[redacted] Central Study Coordinator

The trial was performed according to the Good Clinical Practice guidelines in operation at the time of the initiation of the trial.

Report Date: April 30, 2003

Synopsis of Final Report for Clinical Trial 444563/004 (rota-004)

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Title of the study: A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants approximately 2 months of age and previously uninfected with HRV.

Principal Investigator: Prof. [redacted] Finland

Study sites: The trial was conducted at six sites in Finland.

Publications:

- Efficacy evaluation of an oral human rotavirus (HRV) vaccine in previously uninfected Finnish infants. Poster presented at Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Diego, USA, Sep 27-30, 2002.
- Evaluation of an oral human rotavirus (HRV) vaccine in Europe. Poster presented at World Society for Pediatric Infectious Diseases (WSPID), Santiago, Chile, Nov 18-21, 2002.

Study period:	Date of first visit: August 21, 2000 Data lock point: July 11, 2001	**Clinical phase:** IIb

Note: The synopsis mentions all study objectives, criteria for evaluation and endpoints. However, this final analysis provides results to study objectives pertaining to the period until the end of the first rotavirus (RV) season following vaccination.
Actual viral concentration contained in GSK Biologicals' HRV vaccine (i.e. $10^{4.7}$ ffu) is mentioned.

Objectives:

Primary:

- To determine if two doses of $10^{4.7}$ foci forming units (ffu) of GSK Biologicals' HRV vaccine can prevent RV gastroenteritis (GE) during the period starting from 2 weeks after Dose 2 until the end of the first RV season following vaccination.

Secondary:

Efficacy

- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent severe RV GE during the period starting from the end of the first RV season following vaccination until the end of the second RV season following vaccination.
- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent any and severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.
- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent any and severe GE during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.
- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent asymptomatic RV infections occurring during the period starting from one month after Dose 2 until the end of each RV season following vaccination.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

- To assess if the RV detection method (ELISA versus RT-PCR) modifies vaccine efficacy.
- To characterize the G type of the wild RV strain by RT-PCR.

Safety

- To assess the safety and reactogenicity of two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine versus placebo.
- To assess the presence of RV antigen in any stool samples collected during the time starting from the day of Dose 1 and ending 2 weeks after Dose 2.

Immunogenicity

- To assess the immunogenicity (serum IgA antibody levels) of two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine.

Methodology:
Study design: Double-blind, randomized, placebo-controlled, self-contained study with two parallel groups with unbalanced allocation (2:1 for vaccine:placebo). Parents/guardians were requested to ensure that the subjects did not eat and drink 1 hour before study vaccine administration. Routine vaccinations were to be given 14 days apart from the study vaccine doses.

Number of subjects:

Planned: 405 eligible subjects	Enrolled: 405	Completed: 372 (until Visit 4)
Analyzed for efficacy:	Total cohort: 381 (255 in HRV group and 126 in placebo group)	
	ATP cohort: 368 (245 in HRV group and 123 in placebo group)	
Analyzed for safety:	Total cohort: 400 (267 in HRV group and 133 in placebo group)	
Analyzed for immunogenicity:	Total cohort: 404 (269 in HRV group and 135 in placebo group)	
	ATP cohort: 321 (209 in HRV group and 112 in placebo group)	

Diagnosis and criteria for inclusion: Healthy infants, born after a normal gestation period of 36–42 weeks, 6–12 weeks of age at the time of the first dose of the study vaccination course, free of obvious health problems as established by medical history and clinical examination before entering into the study, and with written informed consent obtained from parents or guardians of the subject.

Test product, dose, mode of administration, lot numbers:

- Each reconstituted dose (1 ml) of GSK Biologicals' HRV vaccine consisted of $10^{4.7}$ ffu of HRV strain, RIX4414 derived from the 89-12 HRV vaccine strain, 9 mg sucrose, 18 mg dextran, 13.5 mg sorbitol and 9 mg amino acids. Lot number DRVC005A46 was used.
  Lot 00C16/1000 was used for the diluent (calcium carbonate 60 mg/ml and xanthane 0.25 % in water for injection).

Mode of administration: Lyophilized HRV vaccine was reconstituted with the supplied diluent and the resuspended product was administered as a single oral dose.

Reference therapy, dose and mode of administration, lot number:

- Each reconstituted dose (1 ml) of GSK Biologicals' placebo consisted of 9 mg sucrose, 18 mg dextran, 13.5 mg sorbitol and 9 mg amino acids. Lot DRVC006A46PL was used.
  Lot 00C16/1000 was used for the diluent (calcium carbonate 60 mg and xanthane 0.25 % in water for injection).

Mode of administration: Lyophilized placebo was reconstituted with the supplied diluent and the resuspended product was administered as a single oral dose.

Duration of treatment: The intended duration of the study, per subject, will be approximately 2 years (approximately 9 months of follow-up until the end of the first RV season and one year follow-up until the end of the second RV season post-vaccination).

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Criteria for evaluation:

Efficacy: Recording of rectal temperature, number of vomiting episodes, number of looser than normal stools passed by the subject, treatment administered and any dehydration during each suspected episode of GE occurring during the period starting from two weeks after Dose 2 and ending at Visit 5 (end of the second RV season after vaccination). Collection of stool samples during each GE episode for RV detection. Episodes were counted as distinct events only if there were > 5 symptom-free days between the episodes. A 20-point scale was used to assess the severity of each GE episode (Ruuska T and Vesikari T, Scand J Infect Dis 1990;22:259-267). A score of < 7 was prospectively defined as mild, a score of 7–10 was prospectively defined as moderate and a score ≥ 11 was prospectively defined as severe (Joensuu J *et al*, Lancet 1997;350:1205-9). Measurement of serum concentration of RV specific IgA antibodies at the end of each RV season (at Visit 4 and Visit 5) to detect asymptomatic RV infection. Seroconversion or ≥ 4-fold rise in anti-rotavirus antibody IgA concentration between one month post Dose 2 and end of the season time point was considered as serological evidence of asymptomatic RV infection.

Primary endpoint:

- Occurrence of RV GE during the period starting from 2 weeks after Dose 2 until the end of the first RV season following vaccination as detected by ELISA in stool samples.

Secondary endpoints:

- Occurrence of RV GE during the period starting from 2 weeks after Dose 2 until the end of the first RV season following vaccination as detected by RT-PCR in stool samples.
- Occurrence of severe RV GE during the period starting from the end of the first RV season until the end of the second RV season following vaccination as detected by ELISA and as detected by RT-PCR in stool samples.
- Occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination as detected by ELISA and as detected by RT-PCR in stool samples.
- Occurrence of any and severe GE during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.
- Occurrence of asymptomatic RV infections during the period starting from 1 month after Dose 2 until the end of each RV season following vaccination.
- G type of the wild RV strain by RT-PCR.

Safety: Recording of solicited symptoms (diarrhea, fever, fussiness/irritability, loss of appetite and vomiting) during the 15-day follow-up period (Day 0 to Day 14) after each study vaccination. Recording of unsolicited symptoms occurring within 42 days after each vaccination and serious adverse events (SAE) during the entire study period. Collection of a stool sample in case of diarrhea and/or vomiting during the period starting from the day of Dose 1 and ending 2 weeks after Dose 2 for RV detection.

Secondary endpoints:

- For each type of solicited symptom, occurrence of the symptom within the 15-day solicited follow-up period after each dose.
- Presence of RV antigen in any stool samples collected during the time starting from the day of Dose 1 and ending 2 weeks after Dose 2.
- Occurrence of unsolicited symptoms within 42 days after each dose, according to World Health Organization's (WHO) classification.
- Occurrence of serious adverse events throughout the entire study period

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Immunogenicity: Measurement of serum concentration of RV specific IgA antibodies at Visit 1 (prior to Dose 1), Visit 3 (1 month after Dose 2), at Visit 4 (at the end of the first RV season) and at Visit 5 (at the end of the second RV season) in all subjects.
Secondary endpoint: Serum anti-rotavirus IgA antibody concentration at each blood sampling timepoint.

Statistical methods:
Efficacy: Efficacy analysis was performed on the According to Protocol (ATP) cohort (primary analysis) and on the total cohort. A global overview of the number of GE episodes and RV GE episodes reported by the subjects from 2 weeks after Dose 2 until end of the first RV season after vaccination on June 1, 2001 was provided for each group. The percentage of subjects reporting RV GE (any and severe intensity) from two weeks after Dose 2 until the end of the first RV season following vaccination was calculated by group with its 95% Confidence Interval (CI).
The percentage of subjects with an asymptomatic RV infection from approximately one month after Dose 2 until the end of the first RV season following vaccination was calculated by group with its 95% CI.
Two-sided Fisher's exact test (significance level of α=0.05) was used to compare these percentages between groups.
The efficacy rate (overall and by type) of the HRV vaccine relative to the placebo was calculated with its 95% CI against RV GE (any and severe intensity) occurring from two weeks after Dose 2 until the end of the first RV season following vaccination. The efficacy rate against asymptomatic RV infection occurring from approximately one month after Dose 2 until the end of the first RV season following vaccination was also calculated.

Safety and reactogenicity:
Safety and reactogenicity analyses were performed only on the total cohort (primary analysis). The percentages of doses and of subjects with any symptom (solicited or unsolicited), with specific solicited symptoms reported during the 15-day follow-up period and with unsolicited symptoms classified by WHO Preferred Term reported during the 43-day follow-up period were tabulated with their exact 95% CI. The same calculations were done for symptoms rated as grade 3 in intensity and those assessed as related to vaccination. The percentage of subjects with RV in stool samples collected in case of diarrhea and/or vomiting from day of Dose 1 till 2 weeks after Dose 2 were tabulated. Differences between groups in terms of the percentage of subjects reporting at least one symptom (solicited or unsolicited), specific solicited symptoms and unsolicited symptoms classified by WHO Preferred Term were explored using the two-sided Fisher's exact test (significance level of α=0.05). Serious Adverse Events (SAEs) and discontinuations due to adverse events were described.

Immunogenicity: Immunogenicity analysis was performed on the ATP cohort (primary analysis) and the total cohort. Geometric Mean Concentration (GMC) and seropositivity rates were calculated with their 95% CI for each group, at each blood sampling time point. The distribution of IgA antibody concentrations one month after Dose 2 were displayed using reverse cumulative curves.

Results: This final analysis was performed on the data obtained until the end of the first RV season post-vaccination. Follow-up during the second RV season was ongoing at the data lock point of this final analysis. Till the end of the study, access to the individual treatment decode will be strictly controlled and restricted to some GSK Biologicals' personnel. Only summary results are provided in this study report and individual subjects' numbers are not specified. The dissemination of the study results will be controlled until study end.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Demographic results: The mean age of the total study cohort at the time of the first study vaccine dose was 8.3 weeks. There were 214 males and 191 females, and the race was listed as white for the majority (99.0%) of subjects. The mean height of the cohort was 58.6 cm and the mean weight was 5.5 kg. The demographic profile of the two groups was comparable with respect to age, gender, race, height and weight.

Efficacy results: The first efficacy follow-up period started 2 weeks after Dose 2 and ended at the end of the first RV season on June 1, 2001. The percentages of subjects reporting RV GE when ELISA was used to detect RV and vaccine efficacy during the first efficacy follow-up period for the ATP efficacy cohort were as follows:

Group	N	Rate			Vaccine efficacy			p-value
		%	95% CI		%	95% CI		
			LL	UL		LL	UL	
HRV	245	3.3	1.4	6.3	69.1	19.6	88.9	0.007
Placebo	123	10.6	5.7	17.4				

N = number of subjects included in each group
Rate = percentage of subjects reporting at least one RV GE episode in each group
95% CI = 95% confidence interval; L.L. = lower limit, U.L. = upper limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

The vaccine efficacy against occurrence of severe (score ≥11 on the 20-point intensity scale) RV GE during the first efficacy follow-up period was 90.0% (95% CI, 10.3 – 99.8) when ELISA was used for detection of RV. A statistically significant decrease in the percentage of subjects reporting any and severe RV GE during the first efficacy follow-up period was detected in the HRV vaccine group as compared to the placebo group ($p < 0.05$, two-sided Fisher's exact test).
When RT-PCR was used for detection of RV, vaccine efficacy against any RV GE was 49.8% (95% CI, -22.2 – 79.4) and vaccine efficacy against severe RV GE was 90.0% (95% CI, 10.3 – 99.8).
The vaccine efficacy against occurrence of asymptomatic RV infection during the period starting from one month after Dose 2 until the end of the first RV season following vaccination was > 94% using either of the RV detection methods (ELISA or RT-PCR). A statistically significant decrease in the percentage of subjects reporting asymptomatic RV infection was detected in the HRV vaccine group as compared to the placebo group ($p < 0.001$, two-sided Fisher's exact test).

Safety results: Irritability was the most commonly reported solicited symptom in both groups. Solicited symptoms rated as grade 3 in intensity were reported at a similar incidence in the two groups.
Statistically significant differences were not detected between the HRV vaccine and the placebo group with respect to the percentage of subjects reporting each solicited symptom within the 15-day follow-up period, except for loss of appetite ($p = 0.046$, two-sided Fisher's exact test).
The percentage of subjects reporting each of the solicited symptoms including those graded "3" in intensity and those considered as related to vaccination, during the 15-day follow-up period for the total cohort were as follows:

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

		HRV vaccine N = 265			Placebo N = 133			
		%	95% CI		%	95% CI		p-value
			LL	UL		LL	UL	
Diarrhea	Total	11.3	7.8	15.8	6.0	2.6	11.5	0.105
	Grade 3	1.9	0.6	4.3	0.0	0.0	2.7	
	Related	9.4	6.2	13.6	3.8	1.2	8.6	
Fever	Total	32.1	26.5	38.1	24.8	17.7	33.0	0.163
	Grade 3	0.4	0.0	2.1	0.0	0.0	2.7	
	Related	19.6	15.0	24.9	12.8	7.6	19.7	
Fussiness/ Irritability	Total	77.0	71.4	81.9	71.4	63.0	78.9	0.269
	Grade 3	8.3	5.3	12.3	9.0	4.7	15.2	
	Related	61.5	55.4	67.4	55.6	46.8	64.2	
Loss of appetite	Total	38.9	33.0	45.0	28.6	21.1	37.0	0.046
	Grade 3	0.4	0.0	2.1	0.0	0.0	2.7	
	Related	27.9	22.6	33.7	18.8	12.5	26.5	
Vomiting	Total	12.8	9.1	17.5	10.5	5.9	17.0	0.625
	Grade 3	4.5	2.4	7.8	1.5	0.2	5.3	
	Related	10.2	6.8	14.5	8.3	4.2	14.3	

N = number of subjects with at least one solicited symptom sheet completed
% = percentage of subjects reporting the specified symptom
95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
p-value = two-sided Fisher's exact test (significant level of α=0.05)

3.4% (6.4%) of the subjects in the HRV vaccine group and none in the placebo group reported at least one RV GE episode during the period starting from the day of Dose 1 and ending 2 weeks after Dose 2, as detected by ELISA (RT-PCR). All these RV positive GE cases were rated as mild or moderate in intensity and were attributed to the G1 strain.
At least one unsolicited symptom was reported from Day 0 to Day 42 after any vaccination by 190 (71.2%) subjects in the HRV vaccine group and 93 (69.9%) subjects in the placebo group. The majority of unsolicited symptoms reported were rated as grade "1" or "2" in intensity.
Eight subjects (6 in the HRV vaccine group and 2 in the placebo group) failed to complete Visit 4 as result of non-serious adverse events. Of these, five subjects had vaccination-related adverse events. Nineteen subjects (15 vaccinees and 4 placebo recipients) reported at least one SAE during the study up to Visit 4; none of these SAEs were assessed as related to study vaccination.

Immunogenicity Results:
Anti-rotavirus IgA antibody GMCs and seropositivity rates by ELISA for the ATP immunogenicity cohort were as follows:

444563/004 Synopsis page 6 of 7

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

			≥ 20 U/ml			GMC (U/ml)		
				95% C.I.			95% C.I.	
Group	**Timing**	**N**	**%**	**L.L**	**U.L**	**Value**	**L.L**	**U.L**
HRV	Pre	209	0.0	0.0	1.7	<20	-	-
	PII(M3)	209	80.4	74.3	85.5	164.0	129.7	207.3
	ES1	189	75.7	68.9	81.6	83.2	67.2	103.0
Placebo	Pre	112	0.0	0.0	3.2	<20	-	-
	PII(M3)	112	0.0	0.0	3.2	<20	-	-
	ES1	106	15.1	8.9	23.4	<20	-	-

N= number of subjects with available data % = percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval L.L. = lower limit, U.L. = upper limit
Pre = Pre-vaccination PII(M3) = one month after the second vaccination ES1 = end of the first RV season

Conclusions:

- This pilot efficacy trial was designed to evaluate the efficacy of GSK Biologicals' HRV vaccine , strain RIX 4414 against RV GE. The efficacy of two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine in decreasing the incidence of RV GE as detected by ELISA relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first RV season following vaccination was demonstrated in healthy infants (6–12 weeks old at study entry) not previously infected with HRV. Thus, the primary objective of the study was met and the proof of concept in terms of clinical protection with a new HRV vaccine strain, RIX 4414, demonstrated.
- GSK Biologicals' HRV vaccine was efficacious in decreasing the incidence of severe RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first RV season following vaccination.
- GSK Biologicals' HRV vaccine was efficacious in decreasing the incidence of asymptomatic RV infections relative to the placebo during the period starting from one month after Dose 2 until the end of the first RV season following vaccination.
- The G1 type was predominant among the wild type RV circulating during the first RV season following vaccination.
- The method (ELISA *versus* RT-PCR) used for detection of RV appeared to influence the estimate of vaccine efficacy against any RV GE but not against severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the first RV season following vaccination.
- GSK Biologicals' HRV vaccine appeared safe when given as a two-dose regimen at a virus concentration of $10^{4.7}$ ffu to healthy infants at 2 and 4 months of age. The reactogenicity profile of the HRV vaccine was similar to that of the placebo in terms of the incidences of solicited and unsolicited symptoms reported after vaccination. No vaccination-related SAEs were reported.
- Gastrointestinal symptoms rated as mild or moderate in intensity were induced in a small proportion of vaccinees as indicated by the presence of RV in stool samples collected in case of GE during the period starting from the day of Dose 1 and ending 2 weeks after Dose 2.
- One month after the 2nd dose, 80.4% of subjects in the HRV vaccine group seroconverted indicating that the vaccine was immunogenic in terms of serum anti-rotavirus IgA antibodies.

Date of report: April 30, 2003

444563/004 Synopsis page 7 of 7

CONTENTS: TEXT

SYNOPSIS OF FINAL REPORT FOR CLINICAL TRIAL 444563/004 (ROTA-004) 2

CONTENTS: TEXT 9

CONTENTS: REPORT TABLES 11

CONTENTS: SUPPLEMENTS 13

CONTENTS: APPENDICES 17

1 INTRODUCTION/RATIONALE 22

2 STUDY OBJECTIVES 22

2.1 PRIMARY OBJECTIVE 22
2.2 SECONDARY OBJECTIVES 23

3 METHODOLOGY 24

3.1 STUDY DESIGN 24
3.2 INVESTIGATORS AND TRIAL CENTERS 25
3.3 ETHICS 25
3.3.1 Protocol amendments/modifications 26
3.4 SELECTION OF STUDY POPULATION 26
3.4.1 Inclusion criteria 26
3.4.2 Exclusion criteria 26
3.4.3 Elimination criteria checked at Visit 2 and Visit 3 27
3.4.4 Elimination criteria checked at Visit 4 and Visit 5 28
3.4.5 Contraindications to vaccination 28
3.5 STUDY VACCINES AND ADMINISTRATION 28
3.5.1 GSK Biologicals' HRV vaccine 28
3.5.2 GSK Biologicals' placebo 29
3.5.3 GSK Biologicals' calcium carbonate buffer used as diluent 29
3.5.4 Dosage and administration 29
3.6 TREATMENT ALLOCATION AND RANDOMIZATION 30
3.7 BLINDING 30
3.8 STUDY PROCEDURES 31
3.9 SUBJECT COMPLETION AND DROP-OUT 32
3.10 ASSESSMENT OF EFFICACY VARIABLES 32
3.10.1 Laboratory assays and timepoints 35
3.11 ASSESSMENT OF SAFETY VARIABLES 35
3.11.1 Pregnancy 39
3.11.2 Prior and concomitant medication 39
3.12 ASSESSMENT OF IMMUNOGENICITY VARIABLES 40
3.12.1 Intervals between study visits 40
3.12.2 Laboratory assays and timepoints 40
3.13 DATA QUALITY ASSURANCE 41
3.14 STATISTICAL METHODS 41
3.14.1 Primary endpoint 42
3.14.2 Secondary endpoints 42

3.14.3 Determination of sample size 43
3.14.4 Study cohorts/data sets analyzed 43
3.14.5 Analysis of demographics 45
3.14.6 Analysis of efficacy 46
3.14.7 Analysis of safety 47
3.14.8 Analysis of immunogenicity 48
3.15 INTERIM ANALYSIS 50
3.16 ANNEX ANALYSIS 50
3.17 CHANGES IN CONDUCT OF THE STUDY/PLANNED ANALYSES 50

4 STUDY POPULATION 52

4.1 STUDY DATES 52
4.2 SUBJECT ELIGIBILITY AND ATTRITION FROM STUDY 52
4.2.1 Number and distribution of subjects 52
4.2.2 Study completion and drop-out 52
4.2.3 Eligibility for analysis 54
4.2.4 Compliance with protocol specified procedures 56
4.3 DEMOGRAPHIC CHARACTERISTICS 57
4.3.1 Subjects included in the ATP efficacy cohort 57
4.3.2 Total cohort 57
4.3.3 Subjects included in the ATP immunogenicity cohort 58

5 ANALYSIS OF EFFICACY 58

5.1 DATA SETS ANALYZED 58
5.2 ACCORDING TO PROTOCOL ANALYSIS 58
5.2.1 Characterization of GE episodes reported during the first efficacy follow-up period58
5.2.2 Vaccine efficacy against RV GE during the first efficacy follow-up period 61
5.2.3 Efficacy against asymptomatic infection during the first efficacy follow-up period63
5.2.4 Vaccine efficacy against hospitalization due to any GE during the first efficacy follow-up period 64
5.3 ANALYSIS OF TOTAL COHORT 64

6 ANALYSIS OF SAFETY 65

6.1 DATA SETS ANALYZED 65
6.2 TOTAL COHORT ANALYSIS 65
6.2.1 Overall incidence of symptoms 65
6.2.2 Solicited signs and symptoms 66
6.2.3 Unsolicited symptoms 70
6.2.4 Concomitant medications/vaccinations 73
6.2.5 Serious Adverse Events 74

7 ANALYSIS OF IMMUNOGENICITY 75

7.1 DATA SETS ANALYZED 75
7.2 ACCORDING TO PROTOCOL ANALYSIS 75
7.2.1 Anti- rotavirus IgA antibody response 75
7.3 ANALYSIS OF TOTAL COHORT 78

8 DISCUSSION 79

9 OVERALL CONCLUSIONS 81

10 REFERENCES 83

11 SUPPLEMENTS.....84

CONTENTS: REPORT TABLES

TABLE 1: CO-INVESTIGATORS, THE GSK BIOLOGICALS' ASSIGNED SITE NUMBERS AND INVESTIGATIONAL SITES.....25
TABLE 2: OUTLINE OF STUDY PROCEDURES.....31
TABLE 3: THE 20-POINT SCALE WAS USED TO ASSESS THE SEVERITY OF EACH GE EPISODE.....34
TABLE 4: SYMPTOMS SOLICITED DURING THE STUDY.....36
TABLE 5: INTERVALS BETWEEN STUDY VISITS*.....40
TABLE 6: ADAPTED INTERVALS BETWEEN STUDY VISITS*.....40
TABLE 7: THE NUMBER OF SUBJECTS ENROLLED AT EACH SITE BY GROUP (TOTAL COHORT).....52
TABLE 8: COUNTS OF SUBJECTS ENROLLED, COMPLETED, DROPPED OUT AND REASON FOR DROP-OUT UNTIL VISIT 4 (TOTAL COHORT).....53
TABLE 9: NUMBER OF SUBJECTS ENROLLED INTO THE STUDY AS WELL AS THE NUMBER OF SUBJECTS EXCLUDED FROM ATP ANALYSES WITH REASONS FOR EXCLUSION.....56
TABLE 10: SUMMARY OF DEMOGRAPHIC CHARACTERISTICS (ATP EFFICACY COHORT).....57
TABLE 11: NUMBER OF GE EPISODES AND RV GE EPISODES REPORTED DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY SEVERITY (ATP EFFICACY COHORT).....59
TABLE 12: PERCENTAGE OF SUBJECTS WITH RV GE EPISODES REPORTED DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY RV G TYPE (ATP EFFICACY COHORT).....60
TABLE 13: PERCENTAGE OF SUBJECTS REPORTING RV GE AND EFFICACY OF THE VACCINE AS MEASURED BY ELISA DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT).....61
TABLE 14: PERCENTAGE OF SUBJECTS REPORTING RV GE (ANY INTENSITY) AND EFFICACY OF THE VACCINE AS MEASURED BY RT-PCR DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT).....62
TABLE 15: PERCENTAGE OF SUBJECTS REPORTING ASYMPTOMATIC RV INFECTION AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT).....63
TABLE 16: NUMBER AND PERCENTAGE OF SUBJECTS WHO RECEIVED VACCINE DOSE(S) (TOTAL COHORT).....65
TABLE 17: PERCENTAGE OF DOSES AND OF SUBJECTS REPORTING SYMPTOMS (SOLICITED OR UNSOLICITED) DURING THE 15-DAY SOLICITED FOLLOW-UP PERIOD (TOTAL COHORT).....66
TABLE 18: PERCENTAGE OF SUBJECTS REPORTING EACH SOLICITED SYMPTOM INCLUDING THOSE GRADED "3" IN INTENSITY AND THOSE CONSIDERED TO BE RELATED TO VACCINATION, DURING THE 15-DAY FOLLOW-UP PERIOD AFTER ANY DOSE (TOTAL COHORT).....67
TABLE 19: PERCENTAGE OF DOSES REPORTING EACH SOLICITED SYMPTOM INCLUDING THOSE GRADED "3" IN INTENSITY AND THOSE CONSIDERED TO BE RELATED TO VACCINATION, DURING THE 15-DAY FOLLOW-UP PERIOD FOR OVERALL DOSES (TOTAL COHORT).....68

TABLE 20: THE PERCENTAGE OF SUBJECTS WITH UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS ASSESSED AS RELATED TO VACCINATION, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL COHORT) 71
TABLE 21: THE PERCENTAGE OF SUBJECTS WITH GRADE 3 UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL COHORT).....72
TABLE 22: SUMMARY OF UNSOLICITED SYMPTOMS RATED AS GRADE 3 IN INTENSITY AND ASSESSED AS RELATED TO VACCINATION FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL COHORT).....73
TABLE 23: NUMBER AND PERCENTAGE OF SUBJECTS WHO TOOK AT LEAST ONE CONCOMITANT MEDICATION FROM DAY 0 TO DAY 14 AFTER EACH VACCINATION, BY TYPE (TOTAL COHORT)74
TABLE 24: ANTI-ROTAVIRUS IGA ANTIBODY GMCS AND SEROPOSITIVITY RATES BY ELISA (ATP IMMUNOGENICITY COHORT).....76
TABLE 25: ANTI-ROTAVIRUS IGA ANTIBODY GMCS CALCULATED ON SUBJECTS SEROPOSITIVE FOR ANTI-ROTAVIRUS IGA ANTIBODIES (ATP IMMUNOGENICITY COHORT) 76
TABLE 26: DIFFERENCE IN PERCENTAGE OF SUBJECTS WHO SEROCONVERTED FOR SERUM ANTI-ROTAVIRUS IGA ANTIBODY ONE MONTH AFTER DOSE 2 BETWEEN HRV VACCINE AND PLACEBO GROUPS (ATP IMMUNOGENICITY COHORT) 77
TABLE 27: DETAILS OF THE RV GE EPISODES REPORTED DURING THE FIRST EFFICACY FOLLOW-UP PERIOD IN SUBJECTS IN THE HRV VACCINE GROUP WHO HAD SEROCONVERTED ONE MONTH AFTER DOSE 2(ATP EFFICACY COHORT) 78

CONTENTS: SUPPLEMENTS

SUPPLEMENT 1: DEVIATIONS FROM SPECIFICATIONS FOR AGE AND INTERVALS BETWEEN STUDY VISITS (TOTAL COHORT) 84
SUPPLEMENT 2: NUMBER OF SUBJECTS AT EACH VISIT AND LIST OF DROPPED-OUT SUBJECTS (TOTAL COHORT) 85
SUPPLEMENT 3: COMPLIANCE (TOTAL COHORT) 87
SUPPLEMENT 4: SUMMARY OF DEMOGRAPHIC CHARACTERISTICS (TOTAL COHORT) 88
SUPPLEMENT 5: SUMMARY OF DEMOGRAPHIC CHARACTERISTICS (ATP IMMUNOGENICITY COHORT) 89
SUPPLEMENT 6: DURATION (IN YEARS) OF THE FOLLOW-UP PERIODS FOR THE FIRST EFFICACY PERIOD (ATP EFFICACY COHORT) 90
SUPPLEMENT 7: NUMBER AND PERCENTAGE OF SUBJECTS WHO REPORTED GE EPISODE(S) DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT) 91
SUPPLEMENT 8: CHARACTERISTICS OF RV GE EPISODES REPORTED DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY ELISA (ATP EFFICACY COHORT) 92
SUPPLEMENT 9: CHARACTERISTICS OF RV GE EPISODES REPORTED DURING FIRST EFFICACY FOLLOW-UP PERIOD, BY RT-PCR (ATP EFFICACY COHORT) 93
SUPPLEMENT 10: PERCENTAGE OF SUBJECTS REPORTING RV GE (ANY INTENSITY) AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY TYPE (ATP EFFICACY COHORT) 94
SUPPLEMENT 11: PERCENTAGE OF SUBJECTS REPORTING SEVERE RV GE AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY TYPE (ATP EFFICACY COHORT) 95
SUPPLEMENT 12: PERCENTAGE OF SUBJECTS HOSPITALIZED DUE TO ANY GE AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT) 96
SUPPLEMENT 13: NUMBER AND PERCENTAGE OF SUBJECTS WHO REPORTED GE EPISODE(S) DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (TOTAL COHORT) 97
SUPPLEMENT 14: NUMBER OF ANY GE EPISODES AND RV GE EPISODES REPORTED DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY SEVERITY (TOTAL COHORT) 98
SUPPLEMENT 15: PERCENTAGE OF SUBJECTS WITH RV GE EPISODES REPORTED DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY TYPE (TOTAL COHORT) 99
SUPPLEMENT 16: CHARACTERISTICS OF RV GE EPISODES REPORTED DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY ELISA (TOTAL COHORT) 100
SUPPLEMENT 17: CHARACTERISTICS OF RV GE EPISODES REPORTED DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY RT-PCR (TOTAL COHORT) 101
SUPPLEMENT 18: DURATION (IN YEARS) OF THE FOLLOW-UP PERIODS FOR THE FIRST EFFICACY PERIOD (TOTAL COHORT) 102
SUPPLEMENT 19: PERCENTAGE OF SUBJECTS REPORTING RV GE (ANY INTENSITY) AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (TOTAL COHORT) 103
SUPPLEMENT 20: PERCENTAGE OF SUBJECTS REPORTING SEVERE RV GE AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (TOTAL COHORT) 104

SUPPLEMENT 21: PERCENTAGE OF SUBJECTS REPORTING RV GE (ANY INTENSITY) AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY TYPE (TOTAL COHORT) .105
SUPPLEMENT 22: PERCENTAGE OF SUBJECTS REPORTING SEVERE RV GE AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY TYPE (TOTAL COHORT) 106
SUPPLEMENT 23: PERCENTAGE OF SUBJECTS HOSPITALIZED DUE TO ANY GE AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (TOTAL COHORT) 107
SUPPLEMENT 24: PERCENTAGE OF SUBJECTS REPORTING ASYMPTOMATIC RV INFECTION AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (TOTAL COHORT)108
SUPPLEMENT 25: PERCENTAGE OF DOSES AND OF SUBJECTS REPORTING SYMPTOMS (SOLICITED OR UNSOLICITED) RATED AS GRADE 3 IN INTENSITY DURING THE 15-DAY SOLICITED FOLLOW-UP PERIOD (TOTAL COHORT) 109
SUPPLEMENT 26: PERCENTAGE OF DOSES AND OF SUBJECTS REPORTING SYMPTOMS (SOLICITED OR UNSOLICITED) ASSESSED AS RELATED TO VACCINATION DURING THE 15-DAY SOLICITED FOLLOW-UP PERIOD (TOTAL COHORT) 110
SUPPLEMENT 27: PERCENTAGE OF DOSES REPORTING EACH SOLICITED SYMPTOM INCLUDING THOSE GRADED "3" IN INTENSITY AND THOSE CONSIDERED TO BE RELATED TO VACCINATION, DURING THE 15-DAY FOLLOW-UP PERIOD AFTER EACH DOSE (TOTAL COHORT) 111
SUPPLEMENT 28: PREVALENCE OF DIARRHEA BY DAY AFTER DOSE 1, DURING THE SOLICITED FOLLOW-UP PERIOD (TOTAL COHORT) 112
SUPPLEMENT 29: PREVALENCE OF DIARRHEA BY DAY AFTER DOSE 2, DURING THE SOLICITED FOLLOW-UP PERIOD (TOTAL COHORT) 113
SUPPLEMENT 30: PREVALENCE OF VOMITING BY DAY AFTER DOSE 1, DURING THE SOLICITED FOLLOW-UP PERIOD (TOTAL COHORT) 114
SUPPLEMENT 31: PREVALENCE OF VOMITING BY DAY AFTER DOSE 2, DURING THE SOLICITED FOLLOW-UP PERIOD (TOTAL COHORT) 115
SUPPLEMENT 32: PREVALENCE OF FEVER BY DAY AFTER DOSE 1, DURING THE SOLICITED FOLLOW-UP PERIOD (TOTAL COHORT) 116
SUPPLEMENT 33: PREVALENCE OF FEVER BY DAY AFTER DOSE 2, DURING THE SOLICITED FOLLOW-UP PERIOD (TOTAL COHORT) 117
SUPPLEMENT 34: DURATION (IN DAYS) OF DIARRHEA DURING THE SOLICITED FOLLOW-UP PERIOD (TOTAL COHORT) 118
SUPPLEMENT 35: DURATION (IN DAYS) OF VOMITING DURING THE SOLICITED FOLLOW-UP PERIOD (TOTAL COHORT) 119
SUPPLEMENT 36: DURATION (IN DAYS) OF FEVER DURING THE SOLICITED FOLLOW-UP PERIOD (TOTAL COHORT) 120
SUPPLEMENT 37: SUMMARY OF SOLICITED GASTROINTESTINAL SYMPTOMS (DIARRHEA AND VOMITING) AND FEVER FOR SUBJECTS WHO REPORTED BOTH DIARRHEA AND VOMITING DURING THE 15-DAY SOLICITED FOLLOW-UP PERIOD (TOTAL COHORT) 121
SUPPLEMENT 38: NUMBER OF GE EPISODES REPORTED FROM DAY OF DOSE 1 TILL DAY 14 AFTER DOSE 2 (TOTAL COHORT).....122

SUPPLEMENT 39: NUMBER OF SUBJECTS REPORTING GE EPISODE FROM DAY OF DOSE 1 TILL DAY 14 AFTER DOSE 2 (TOTAL COHORT) 123
SUPPLEMENT 40: NUMBER OF GE EPISODES REPORTED FROM DAY OF DOSE 1 TILL DAY 14 AFTER DOSE 2, BY STOOL RESULTS (TOTAL COHORT) 124
SUPPLEMENT 41: NUMBER OF SUBJECTS REPORTING RV GE EPISODE FROM DAY OF DOSE 1 TILL DAY 14 AFTER DOSE 2 (TOTAL COHORT) 125
SUPPLEMENT 42: SUMMARY OF RV GE EPISODES AS DETECTED BY ELISA DURING THE PERIOD STARTING FROM THE DAY OF DOSE 1 AND ENDING 2 WEEKS AFTER DOSE 2 (TOTAL COHORT) 126
SUPPLEMENT 43: SUMMARY OF RV GE EPISODES AS DETECTED BY RT-PCR DURING THE PERIOD STARTING FROM THE DAY OF DOSE 1 AND ENDING 2 WEEKS AFTER DOSE 2 (TOTAL COHORT) 127
SUPPLEMENT 44: NUMBER OF RV GE EPISODES IN THE HRV VACCINE GROUP, FROM DAY OF DOSE 1 TILL DAY 14 AFTER DOSE 2, BY SEVERITY (TOTAL COHORT) 128
SUPPLEMENT 45: THE PERCENTAGE OF SUBJECTS WITH UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL COHORT) 129
SUPPLEMENT 46: THE PERCENTAGE OF DOSES WITH UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS ASSESSED AS RELATED TO VACCINATION, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL COHORT) 135
SUPPLEMENT 47: THE PERCENTAGE OF DOSES WITH GRADE 3 UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL COHORT) 136
SUPPLEMENT 48: THE PERCENTAGE OF DOSES WITH UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL COHORT) 138
SUPPLEMENT 49: THE PERCENTAGE OF SUBJECTS WITH GASTROINTESTINAL SYMPTOMS (UNSOLICITED SYMPTOMS), FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL COHORT) 143
SUPPLEMENT 50: THE PERCENTAGE OF DOSES WITH GASTROINTESTINAL SYMPTOMS (UNSOLICITED SYMPTOMS), FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL COHORT) 144
SUPPLEMENT 51: PERCENTAGE OF SUBJECTS WHO STARTED TAKING ANTIPYRETIC AFTER DOSE 1, BY DAY FROM DAY 0 TO DAY 42 (TOTAL COHORT) 145
SUPPLEMENT 52: PERCENTAGE OF SUBJECTS WHO STARTED TAKING ANTIPYRETIC AFTER DOSE 2, BY DAY FROM DAY 0 TO DAY 42 (TOTAL COHORT) 146
SUPPLEMENT 53: DISTRIBUTION OF ANTI-ROTAVIRUS IGA ANTIBODY CONCENTRATIONS (ATP IMMUNOGENICITY COHORT) 147
SUPPLEMENT 54: REVERSE CUMULATIVE DISTRIBUTION CURVE FOR ANTI-ROTAVIRUS IGA ANTIBODY CONCENTRATIONS ONE MONTH AFTER DOSE 2, IN THE HRV VACCINE GROUP (ATP IMMUNOGENICITY COHORT) 148
SUPPLEMENT 55: PERCENTAGE OF SUBJECTS IN THE HRV VACCINE GROUP REPORTING RV GE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY STATUS OF ANTI-ROTAVIRUS IGA ANTIBODY CONCENTRATION AT VISIT 3 (ATP EFFICACY COHORT) 149

SUPPLEMENT 56: ANTI-ROTAVIRUS IGA ANTIBODY GMC AND SEROPOSITIVITY RATES (TOTAL COHORT).....150
SUPPLEMENT 57: DISTRIBUTION OF ANTI-ROTAVIRUS IGA ANTIBODY CONCENTRATIONS (TOTAL COHORT).....151
SUPPLEMENT 58: ANTI-ROTAVIRUS IGA ANTIBODY GMC CALCULATED ON CALCULATED ON SUBJECTS SEROPOSITIVE FOR ANTI-ROTAVIRUS IGA ANTIBODIES (TOTAL COHORT) 152

CONTENTS: APPENDICES

APPENDIX A: CLINTRIAL ELIGIBILITY CODES 153
APPENDIX B: MATHEMATICAL DETAILS* ABOUT THE COMPUTATION OF THE 95%CI FOR VACCINE EFFICACY 155

INDIVIDUAL DATA LISTING NOT PROVIDED SINCE THIS DOUBLE-BLIND STUDY IS STILL ONGOING.

APPENDICES: SERIOUS ADVERSE EVENTS

- SERIOUS ADVERSE EVENTS CASE NARRATIVES
- SERIOUS ADVERSE EVENTS TABLE

APPENDICES: STUDY INFORMATION

- PROTOCOL
- REPRESENTATIVE SUBJECT INFORMATION SHEET
- RELEVANT PAGES OF CRF (UNIQUE PAGES ONLY)
- ONE PAGE CV FOR PRINCIPAL INVESTIGATOR(S)
- REPORT ANALYSIS PLAN
- PUBLICATIONS REFERENCED IN THE REPORT

List of Abbreviations

ATP	According to Protocol
CI	Confidence Interval
cm	Centimeter
CRF	Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
ES	End of season
ffu	Foci forming units
GCP	Good Clinical Practice
GE	Gastroenteritis
GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline
HRV	Human Rotavirus
HIV	Human Immunodeficiency Virus
Kg	Kilogram
LL	Lower limit
ml	Milliliter
RAP	Report Analysis Plan
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious Adverse Event
SARR	Suspect Adverse Reaction Report
SAS	Statistical Analysis System
SD	Standard Deviation
U	Units
USA	United States of America
UL	Upper limit
WHO	World Health Organization

Glossary of Terms

According to protocol cohort:	Includes all subjects enrolled in the study who met the criteria defined in the protocol for the considered analysis (efficacy, reactogenicity or immunogenicity).
Adverse event:	Any noxious, pathologic or unintended change in anatomical, physiologic and/or laboratory detected changes occurring in any phase of the clinical trial whether associated with vaccination or whether or not considered vaccine related.
Asymptomatic rotavirus infections:	Seroconversion (for subjects negative for anti-rotavirus IgA antibody concentration at Visit 3) or ≥ 4-fold increase in IgA antibody concentrations (for subjects positive for anti-rotavirus IgA antibody concentration at Visit 3) between one month after dose 2 (Visit 3) and each end of season sampling time points in subjects who did not report a rotavirus GE episode between one month after Dose 2 and each end of season sampling time points.
Case report form:	Hard copy standardized form for recording individual subject data.
Completed:	Subject who completed the final study visit.
Diarrhea:	Three or more looser than normal stools within a day.
Diary card:	Individual card provided by the sponsor for each vaccinee after each vaccine dose designed to document the presence of solicited adverse events as well as any other sign/symptom the vaccinee might experience.
Documented dose:	Any dose with a symptom sheet completed and/or at least one unsolicited symptom reported.
Drop-out:	Subject who did not return for the final study visit.

	For this study report, subjects who did not return at Visit 4 were assessed as drop-outs.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled:	Participated in the first visit of the study after written informed consent obtained from parents/guardians, determined to be eligible for inclusion in the study based upon strict adherence to inclusion/exclusion criteria and received vaccination.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in analysis.
Gastroenteritis:	Diarrhea and/or vomiting.
Rotavirus gastroenteritis for efficacy analysis:	An episode of gastroenteritis occurring at least two weeks after Dose 2 in which rotavirus was identified by ELISA (RT-PCR) in a stool sample collected during an episode of gastroenteritis. Stool samples collected from the start of the gastroenteritis episode to the minimum of the following 2 timepoints either 7 days after the end of the gastroenteritis episode or the day before the next gastroenteritis episode, if subject had several episodes of gastroenteritis were taken into account.
Separate episodes of gastroenteritis:	Two occurrences of gastrointestinal symptoms with 5 or more symptoms-free days between the episodes.
Seroconversion:	Appearance of anti-rotavirus IgA antibody concentration ≥ 20 U/ml in subjects initially (i.e. prior to the first dose) negative for rotavirus.
Seronegative:	A subject whose antibody concentration was below the assay cut-off value.

Seropositive:	A subject whose antibody concentration was greater than or equal to the assay cut-off value.
Severe rotavirus gastroenteritis:	An episode of rotavirus gastroenteritis with score ≥ 11 on a 20 point scoring system.
Subject(s)/Vaccinee(s):	Terms used throughout the report to denote the enrolled/vaccinated individual(s).
Symptom sheets:	The specific pages in the individual case report forms onto which the investigator transcribed diary card documentation on solicited symptom(s) reported for the subject.
Total cohort:	All enrolled subjects for whom data were available.
Vomiting:	One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

1 Introduction/Rationale

An attenuated human rotavirus (HRV) vaccine candidate was developed from the 89-12 human rotavirus strain belonging to the serotype G1P1A and genotype [P8]. Initial development of the 89-12 vaccine at passage 33 has demonstrated its safety, immunogenicity and efficacy in infants ([1], [2]). GlaxoSmithKline (GSK) Biologicals has implemented several process changes to the 89-12 vaccine candidate at passage 33 to develop a lyophilized HRV vaccine containing a cloned 89-12 HRV strain at passage 43, referred to as RIX4414.

This study was undertaken to assess the efficacy, reactogenicity, safety and immunogenicity of GSK Biologicals' HRV vaccine in the target age group - infants approximately 2 months of age who were previously uninfected with HRV.

The efficacy, reactogenicity, safety and immunogenicity results obtained until the end of the first rotavirus (RV) season following vaccination are presented in this study report.

Data from the end of the first RV season until study end (second consecutive RV season) will be presented in an annex report.

.

2 Study Objectives

Note: Although all study objectives are listed below, only objectives pertaining to the period until the end of the first RV season following vaccination are addressed in this study report. Actual viral concentration contained in GSK Biologicals' HRV vaccine is mentioned.

2.1 Primary objective

- To determine if two doses of $10^{4.7}$ foci forming units (ffu) of GSK Biologicals' HRV vaccine can prevent RV gastroenteritis (GE) during the period starting from 2 weeks after Dose 2 until the end of the first RV season following vaccination.

Refer to the glossary of terms for definition of terms used.

See Section 3.14.1 for delineation of the primary endpoint.

2.2 Secondary objectives

Efficacy

- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent severe RV GE during the period starting from the end of the first RV season following vaccination until the end of the second RV season following vaccination.

- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent any and severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.

- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent any and severe GE during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.

- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent asymptomatic RV infections occurring during the period starting from one month after Dose 2 until the end of each RV season following vaccination.

- To assess if the RV detection method (ELISA versus RT-PCR) modifies vaccine efficacy.

- To characterize the G type of the wild RV strain by RT-PCR.

Safety

- To assess the safety and reactogenicity of two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine versus placebo.

- To assess the presence of RV antigen in any stool samples collected during the time starting from the day of Dose 1 and ending 2 weeks after Dose 2.

Immunogenicity

- To assess the immunogenicity (serum IgA antibody levels) of two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine.

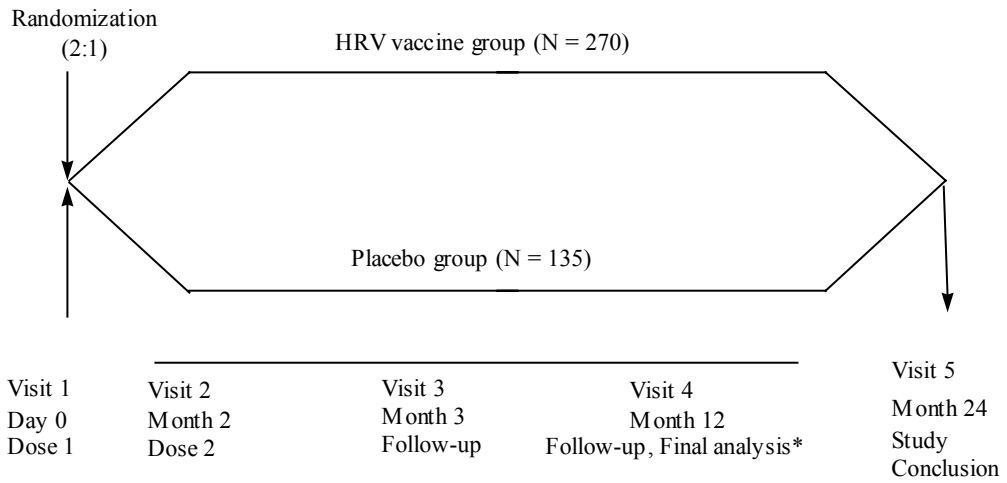
See Section 3.14.2 for delineation of secondary endpoints.

3 Methodology

Appendices: Study Information contains the study protocol, a representative subject information sheet and unique pages of the individual case report form (CRF) utilized in the study.

3.1 Study design

Experimental design



* on data collected until the end of first RV season

This was a double-blind, randomized, placebo-controlled, self-contained study consisting of two parallel groups with unbalanced allocation (2:1 for vaccine:placebo). Blinding will be maintained until study end at Visit 5. Refer to Section 3.7 for information on maintenance of study blind.

Parents/guardians were requested to ensure that the subjects did not eat and drink one hour before study vaccine administration. The protocol specified that routine vaccinations were to be given 14 days apart from the study vaccine doses.

The intended duration of the study, per subject, was approximately 2 years (approximately 9 months follow-up until the end of the first RV season and one year follow-up until the end of the second RV season).

3.2 Investigators and trial centers

Appendices: Study Information contains the *curriculum vitae* of the principal investigator.

The principal investigator is Prof. [redacted] and his address is [redacted] Finland.

The study was conducted at six sites in Finland. Dr. [redacted] at the [redacted] Finland was the co-ordinating investigator for all study sites. Table 1 provides information regarding the co-investigators who participated in the study.

Table 1: Co-investigators, the GSK Biologicals' assigned site numbers and investigational sites

Site No	Co-investigators	Investigational site
[redacted]	Dr. [redacted]	[redacted] Finland
[redacted]	Dr. [redacted]	[redacted] Finland
[redacted]	Dr. [redacted]	[redacted] Finland
[redacted]	Dr. [redacted]	[redacted] Finland
[redacted]	Dr. [redacted]	[redacted] Finland
[redacted]	Dr. [redacted]	[redacted] Finland

3.3 Ethics

The study was conducted according to Good Clinical Practice (GCP) and in accordance with the Declaration of Helsinki as amended in Somerset West, Republic of South Africa, October 1996.

The study protocol dated May 26, 2000 and the statement of informed consent were approved by the [redacted]

Written informed consent was obtained from each subject's parent or guardian prior to entry into the study.

Standardized hard copy CRFs were provided for each subject's data to be recorded.

3.3.1 Protocol amendments/modifications

The protocol was amended on March 25, 2002 to implement the following

- presentation of the results obtained until Visit 4 (end of the first RV season) in a summary form at medical congresses, and
- additional testing of GE stool samples that were negative for RV by RT-PCR to detect the presence of other gastrointestinal viruses in order to establish the etiology of the gastrointestinal symptoms for the research interest of the principal investigator. This additional testing of the stool samples was the responsibility of the principal investigator and the results of the analyses will not be described in the annex study report written after study end.

3.4 Selection of study population

The study population consisted of 405 healthy male and female infants enrolled in the study sites mentioned above. Inclusion/exclusion criteria were checked at study entry.

3.4.1 Inclusion criteria

- A male or female between, and including, 6 and 12 weeks of age at the time of the first vaccination.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Written informed consent obtained from the parents or guardians of the subject.
- Born after a normal gestation period (between 36 and 42 weeks).

3.4.2 Exclusion criteria

- Use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the study vaccine or placebo or planned use during the study period.
- Planned administration of a vaccine (including routine paediatric vaccines) not foreseen by the study protocol during the period starting from 14 days before each dose of vaccine and ending 14 days after.

- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth. (Topical steroids were allowed.)
- Use of antibiotics during the period starting from 7 days before each dose of vaccine and ending 7 days after.
- Any clinically significant history of chronic gastrointestinal disease or other serious medical condition as determined by the investigator.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
- History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.
- Acute disease at time of enrolment. (Acute disease was defined as the presence of moderate or severe illness with fever i.e. temperature ≥ 100.4°F (≥ 38.0°C) as measured by a rectal thermometer).
- GE within 7 days preceding the study vaccine administration (warrants deferral of the vaccination).
- Household contact with an immunosuppressed individual or pregnant woman.
- Abnormal stool pattern (typically ≥ 3/day or < 3/week without the use of laxatives or anti-diarrheal agents).
- Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
- Previous confirmed occurrence of RV GE.

3.4.3 Elimination criteria checked at Visit 2 and Visit 3

The following criteria were checked at Visits 2 and 3. The occurrence of any of these events did not serve as a requirement to discontinue the study but served as an indication for possible elimination from analyses (see Section 3.14.4 for description of analysis cohorts).

- Use of any investigational or non-registered drug or vaccine other than the study vaccine during the study period.
- Use of antibiotics during the period starting from 7 days before each dose of vaccine and ending 7 days after.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
- Administration of a vaccine (including routine paediatric vaccines) not foreseen by the study protocol during the period starting from 14 days before each dose of vaccine(s) and ending 14 days after.
- Administration of immunoglobulins and/or any blood products during the study period.

3.4.4 Elimination criteria checked at Visit 4 and Visit 5

The following criteria were checked at Visit 4 and Visit 5. The occurrence of any of these events did not serve as a requirement to discontinue the study but served as an indication for possible elimination from analyses (see Section 3.14.4 for description of analysis cohorts).

- Use of any investigational or non-registered drug or vaccine other than the study vaccine during the study period.

3.4.5 Contraindications to vaccination

The following adverse events constituted absolute contraindications to further administration of vaccine or placebo; if any of these adverse events occurred during the study, the subject did not receive additional doses of vaccine or placebo but could continue other study procedures at the discretion of the investigator. The subject was followed until resolution of the event, as with any adverse event:

- Hypersensitivity reaction due to the vaccine.

The following adverse events constituted contraindications to administration of vaccine or placebo at that point in time; if any one of these adverse events occurred at the time scheduled for vaccination, the subject could be vaccinated at a later date, within the time window specified in the protocol, or withdrawn at the discretion of the investigator. The subject was followed until resolution of the event, as with any adverse event:

- Rectal temperature ≥ 100.4°F (38°C)
- GE within 7 days preceding the study vaccine administration.

3.5 Study vaccines and administration

The vaccines used in this study were developed and manufactured by GSK Biologicals, Belgium.

The Quality Control Standards and Requirements for each vaccine are described in separate release protocols and the required approvals were obtained. The vaccine release protocols are archived in the study file and are available upon request.

3.5.1 GSK Biologicals' HRV vaccine

One dose of lyophilized vaccine contained the following components:

RIX4414 (derived from the 89-12 HRV strain)	$10^{4.7}$ ffu

Sucrose	9 mg
Dextran	18 mg
Sorbitol	13.5 mg
Amino acids	9 mg

Lot number DRVC005A46 was used.

3.5.2 GSK Biologicals' placebo

One dose of lyophilized placebo contained the following components:

Sucrose	9 mg
Dextran	18 mg
Sorbitol	13.5 mg
Amino acids	9 mg

Lot number DRVC006A46PL was used.

3.5.3 GSK Biologicals' calcium carbonate buffer used as diluent

Each pre-filled syringe of 1.3 ml in volume contained the following components per 1.0 ml:

Calcium carbonate	60 mg
Xanthane 0.25 % in water for injection	1.0 ml

Lot number 00C16/1000 was used.

3.5.4 Dosage and administration

All subjects were required not to eat and drink one hour before study vaccine administration.

To prepare the vaccine or placebo for administration, the entire contents of the pre-filled syringe containing the diluent (approximately 1.3 ml) was used to reconstitute the lyophilized product contained in a monodose vial. The vial was to be shaken well to resuspend the pellet. It is estimated that at least 1.0 ml of the reconstituted vaccine is administered as a single oral.

The subjects were observed closely for at least 30 minutes, with appropriate medical treatment readily available, in case of a rare anaphylactic reaction following the administration of vaccine.

3.6 Treatment allocation and randomization

Assuming on the basis of other studies in a similar population that 10% of enrolled subjects would not be evaluable for analysis of the primary objective, target enrolment was 405 subjects (270 in the HRV vaccine group and 135 in the placebo group) in order to have 360 evaluable subjects (240 subjects in the HRV vaccine group and 120 in placebo group) for the analysis of the primary objective.

A randomization list was prepared by the sponsor using a standard SAS® (Statistical Analysis System) program. A total of 405 subjects were randomly allocated to two groups. A randomization blocking scheme (2:1 ratio for vaccine:placebo) was used to ensure that balance between treatments was maintained. A randomization or subject number identified uniquely the vaccine dose to be administered to each subject. The vaccine doses were distributed to the study sites respecting the randomization block size.

On Day 0, subjects were administered the vaccine dose with the lowest number available at the study site. The randomization (or subject) number was also used as subject identification for all data collected during the study.

3.7 Blinding

The study was conducted in a double-blind manner so that parents/guardians of the subjects and the study personnel were unaware of the administered treatment.

A set of individual codes was held at the local GSK Biologicals' Safety Office and GSK Biologicals' Central Safety Office. The code was broken by the Clinical Safety physician only in the case of medical events, which the investigator/physician in charge of the subject felt, could not be treated without knowing the identity of the study vaccine. In the event that the code was broken, the reason was recorded in the CRF and in the subject's medical record.

During analysis at the end of the first RV season, only the statistician, database administrator and medical writer (only for SAEs) had access to the individual treatment code. After completion of the analysis at the end of the first RV season, access to the treatment code for subjects with RV GE was given to the Clinical Development Manager and Director as described in Section 3.17. No other dissemination of the treatment code will be provided until study end. Only summary results are provided in this study report and individual subjects' numbers are not specified. The dissemination of the study results will be controlled until study end.

3.8 Study procedures

The study procedures carried out at each visit are given in Table 2.

Table 2: Outline of study procedures

Age Visit Timing Sampling timepoint	6–12 weeks **VISIT 1** Day 0 Pre	**VISIT 2** Month 2	**VISIT 3** Month 3 Post Vacc 2	**VISIT 4†** June 2001 ES1	**VISIT 5‡** June 2002 ES2
Informed consent	•				
Medical history	•				
Check of inclusion criteria	•				
Check of exclusion criteria	•				
Check of elimination criteria		•	•	•	•
Check of contraindications	•	•			
Randomization	•				
Physical examination	•	•	•	•	•
Pre-vaccination body temperature	•	•			
Measure/record height and weight	•				
Blood sampling (1ml of whole blood)	•		•	•	•
Vaccination	•	•			
Daily post-vaccination recording of solicited symptoms (Day 0 to Day 14) by parents/guardians	•	•			
Collection of stool samples		•	•	•	•
Return frozen stool samples		•	•	•	•
Recording of non-serious adverse events (unsolicited symptoms) within 42 days after each dose, by investigator		•	•		
Return of diary cards for solicited and unsolicited symptoms		•	•		
Return of diary cards for GE symptoms			•	•	•
Diary card transcription		•	•	•	•
Recording medication	•	•	•		
Reporting of Serious Adverse Events occurring throughout the study, by investigator		•	•	•	•
Study Conclusion					•

Source: Protocol and sample CRF in *Appendices: Study Information*
Notes: ES1 = End of first RV season
ES2 = End of second RV season
Comments: † Visit 4 took place after the end of the first RV season; ‡ Visit 5 was planned to take place after the end of the second RV season

3.9 Subject completion and drop-out

From an analysis perspective, a 'drop-out' was any subject who did not come back for the concluding visit foreseen in the protocol. A subject who returned for the concluding visit foreseen in the protocol was considered to have completed the study.

For this final analysis, a subject who did not return at Visit 4 was considered as a drop-out.

Investigators attempted to contact those subjects who did not return for scheduled visits or follow-up. Information gathered was described on the Study Conclusion page of the CRF and on Medication/Adverse event forms. The possible reasons responsible for drop-out of the subject from the study were specified on the Study Conclusion page of the CRF and were as follows:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (specify)
- Consent withdrawal, not due to an adverse event
- Migration from the study area
- Lost to follow-up
- Other (specify)

Study drop-outs were not replaced.

3.10 Assessment of efficacy variables

GE follow-up diary cards were provided to the parents/guardians of the subjects at Visit 2, Visit 3 and Visit 4 to record specific symptoms during any suspected GE episodes occurring from two weeks after the Dose 2 until the end of the second RV season after vaccination. GE was defined as diarrhea and/or vomiting.

The RV season in Finland is expected from December to June of each year. During each RV season, a study nurse was to contact the parents/guardians by telephone approximately every two weeks to check on the subject's health and the occurrence of any GE symptoms.

Follow-up visits were planned at the end of each RV season. Follow-up visit at the end of the first RV season (Visit 4) occurred between May 30 and July 11, 2001. However, only GE episodes occurring until June 1, 2001 were included in the efficacy analysis of the first RV season. Visit 5 at the end of the second RV season was planned to take place between June 1 and June 30, 2002.

On each day during a suspected episode of GE occurring during the period starting from two weeks after Dose 2 until Visit 5, the parents/guardians were asked to record the following on the GE follow-up diary cards until symptoms resolved: rectal temperature, number of vomiting episodes, and number of looser than normal stools passed by the subject. The parents/guardians were instructed to return their completed diary cards to the investigator at the following study visit. The treatment given and any dehydration were also recorded. The investigator checked the completed diary cards and transcribed data into the appropriate sections of the CRFs.

Parents/guardians were instructed to collect stool sample(s) during the entire study period if the subject developed diarrhea and/or vomiting. Parents/guardians were given instructions to be followed for appropriate collection, storage and transportation of the stool samples. In case of GE episode occurring from the day of administration of Dose 1 until 2 weeks after Dose 2, stool samples were to be collected preferably at the onset of symptoms. The protocol specified that in case of GE episode occurring from 2 weeks after Dose 2, stool samples were to be collected not later than 7 days after the start of symptoms. If GE symptoms lasted for only one day, one stool sample was to be collected. For each GE episode lasting more than one day, at least 2 stool samples were to be collected on 2 different days. The time interval for stool sampling was adapted prior to analysis. Stool samples collected from the start of the GE episode to the minimum of the following 2 timepoints either 7 days after the end of the GE episode or the day before the next GE episode if subject had several episodes of GE were used to identify an episode of RV GE. Only episodes of GE occurring during the period starting two weeks after Dose 2 until June 1, 2001 were included in the efficacy evaluation of the first RV season.

The parents/guardians were instructed to contact the study nurse/investigator by telephone whenever they suspected that the subject had GE during the period starting from 2 weeks after Dose 2 until Visit 5 and notify the study personnel of the symptoms. The parents/guardians were also instructed to contact the study nurse/investigator immediately if the subject manifested any signs or symptoms they perceived as serious.

During GE episodes occurring from 2 weeks after Dose 2 until Visit 5, study personnel contacted the parents/guardians by telephone or other convenient method every day till symptoms resolved to check on the subjects' health. The investigator or his staff determined during the telephone contact whether or not the child needed to be examined at the clinic. If determined necessary during the telephone contact, the parents/guardians were asked to visit the investigator's clinic preferably on the same day for examination and treatment.

A 20-point scale was used to assess the severity of each GE episode ([3]). Refer to Table 3 for the scoring system used to assess the severity of each GE episode (data collected *via* diary cards by the parents/guardians). Points were assigned at GSK Biologicals according to duration and intensity of diarrhea and vomiting, the intensity of fever, presence of dehydration or hospitalization for each episode of GE. Subjects with only fever did not receive a score.

Table 3: The 20-point scale was used to assess the severity of each GE episode

Adverse Experience	Points
Duration of looser than normal stools (days)	
1 – 4	1
5	2
≥ 6	3
Maximum number of looser than normal stools/24 hours	
1 – 3	1
4 – 5	2
≥ 6	3
Duration of vomiting (days)	
1	1
2	2
≥ 3	3
Maximum number of episodes of vomiting/24 hours	
1	1
2 – 4	2
≥ 5	3
Fever (measured rectally)*	
37.1 – 38.4°C	1
38.5 – 38.9°C	2
≥ 39°C	3
Treatment	
Oral rehydration	1
Hospitalization	2
Dehydration	
1 – 5 %	2
≥ 6%	3

Comments: * The highest temperature recorded during the episode was scored. Subjects with fever only did not receive a score.

A score of < 7 was prospectively defined as mild, a score of 7–10 was prospectively defined as moderate and a score ≥ 11 was prospectively defined as severe ([4]).

Serum concentration of RV specific IgA antibodies were measured by ELISA at the end of each RV season (at Visit 4 and Visit 5) to detect asymptomatic RV infection. Seroconversion or ≥ 4-fold rises of anti-rotavirus antibody IgA concentration between one month post Dose 2 and end of the season time point was considered as a serological evidence of an asymptomatic RV infection.

3.10.1 Laboratory assays and timepoints

Stool sampling

The protocol specified that all stool samples collected during any episodes of diarrhea and/or vomiting were to be analyzed by ELISA at the Laboratory of Dr. [redacted] Children's Hospital Medical Center, Cincinnati, USA ([1], [2]) and by RT-PCR at the Laboratory of Prof. [redacted] Finland ([5], [6]) to detect the presence of RV. If RV was detected in the stool specimens, the specimens were to be analyzed by RT-PCR to determine the G type at the Laboratory of Prof. [redacted] Finland.

Please refer to Section 3.17 for details on the changes made to the protocol-specified stool testing plan.

3.11 Assessment of safety variables

Pre-existing conditions, signs and/or symptoms (including any which were not recognized at study entry but were recognized during the study period) present in a subject prior to the start of the study were recorded on the Medical History Form within the subject's CRF. Adverse events which occurred after informed consent was obtained, but prior to vaccination, were also documented in the Medical History Form within the subject's CRF.

At each visit/assessment, all adverse events either observed by the investigator or one of his clinical collaborators or reported by the subject spontaneously or in response to a direct question were evaluated by the investigator. Adverse events not previously documented in the study were recorded in the Adverse Event Form within the subject's CRF. Details of any corrective treatment were recorded on the appropriate page of the CRF. Adverse events already documented in the CRF, i.e. at a previous assessment, and designated as 'ongoing' were reviewed at subsequent visits, as necessary. If these had resolved, the documentation in the CRF was completed.

The parents/guardians were instructed to contact the investigator immediately if the subject manifested any signs or symptoms during the study that they perceived as serious.

On the day of each study vaccination, diary cards were distributed to the parents/guardians to record solicited adverse events occurring during the 15-day (Day 0 to Day 14) solicited follow-up period and unsolicited symptoms occurring during the 43-day (Day 0 to Day 42) follow-up period after each vaccination. See Table 4 for adverse events solicited during the study.

Table 4: Symptoms solicited during the study

Adverse Experience	**Intensity grade**	**Parameter**
Diarrhea		Number of looser than normal stools/day recorded
Fever*		Temperature recorded in °C using a rectal/oral thermometer
Fussiness / Irritability	0	Behaviour as usual
	1	Crying more than usual/ no effect on normal activity
	2	Crying more than usual/ interferes with normal activity
	3	Crying that cannot be comforted/ prevents normal activity
Loss of appetite	0	Normal
	1	Eating less than usual/ no effect on normal activity
	2	Eating less than usual/ interferes with normal activity
	3	Not eating at all
Vomiting		Number of vomiting episodes/day recorded.

Comments: *Rectal temperature was recorded in the evening. If temperature measurement was performed additionally at another time of day, the highest temperature was recorded.

On Day 14 after each dose, a study nurse contacted the parents/guardians, by telephone or other convenient method, and reminded them to bring the completed diary card at the next visit. When completed and returned, diary cards were checked by the investigator and data transcribed into the appropriate sections of the CRFs, i.e., symptom sheets or adverse event sections.

The maximum intensity of fever, diarrhea and vomiting were scored at GSK Biologicals as follows:

Diarrhea	0	:	0 – 2 looser than normal stools/day
	1	:	3 looser than normal stools/day
	2	:	4 – 5 looser than normal stools/day
	3	:	≥ 6 looser than normal stools/day

Fever			Measured rectally	Measured orally
	0	:	< 38.0°C	< 37.5°C
	1	:	≥ 38.0 – ≤ 38.5°C	≥ 37.5 – ≤ 38.0°C
	2	:	> 38.5 – ≤ 39.5°C	> 38.0 – ≤ 39.0°C

	3	:	> 39.5°C	> 39.0°C

Vomiting	0	:	No emesis
	1	:	1 episode of vomiting/day
	2	:	2 episodes of vomiting/day
	3	:	≥ 3 episodes of vomiting/day

For all other (unsolicited) adverse events, maximum intensity was assigned to one of the following categories:

1 : An adverse event which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2 : An adverse event which was sufficiently discomforting to interfere with normal everyday activities.

3 : An adverse event which prevented normal, everyday activities. (Such an adverse event would, for example, prevented attendance at school/ kindergarten/ a day-care centre and caused the parents/ guardians to seek medical advice.)

Every effort was made by the investigator to explain each adverse event and assess its causal relationship, if any, to administration of the study vaccine. The degree of certainty with which an adverse event could be attributed to administration of the study vaccines (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) was determined by how well the event could be understood in terms of one or more of the following:

- Reaction of similar nature having previously been observed with this type of vaccine and/or formulation.
- The event having often been reported in literature for similar types of vaccines.
- The event being temporally associated with vaccination or reproduced on re-vaccination.

Causality of all adverse events was assessed by the investigator using the following method:
In your opinion, did the vaccines possibly contribute to the adverse event?

NO : The adverse event was not causally related to administration of the study vaccine. There were other, more likely causes and administration of the study vaccine was not suspected to have contributed to the adverse event.

YES : There was a reasonable possibility that the vaccine contributed to the adverse event.

If an event met the criteria to be determined "serious" (see below for definition of serious adverse event), it was examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each serious adverse event (SAE). Other possible contributors included:

- Medical history
- Other medication
- Protocol required procedure
- Lack of efficacy of the vaccine
- Erroneous administration
- Other cause (to be specified)

A SAE was defined as any untoward medical occurrence that:

- resulted in death
- was life threatening
- resulted in persistent or significant disability/incapacity
- required in-patient hospitalization or prolongation of hospitalization
- was a congenital anomaly/birth defect in the offspring of a subject.

In addition, any important medical event that might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above was also considered as serious.

The investigator was required to notify GSK Biologicals of any SAE starting from the day of administration of the first dose of study vaccines to each subject and ending at study end within 24 hours of his/her becoming aware of the event. Following the telephone report, a full written report was to be provided which included all relevant supporting documentation such as hospital records, eventual post-mortem reports and/or other documents where applicable.

Treatment of any adverse event was at the discretion of the investigator and according to current GCP. Treatment measures were reported in the appropriate pages of the CRF. The investigator was to follow subjects with SAEs until the event subsided or until the condition stabilized. The investigator was to follow subjects with non-serious adverse events until study conclusion for that subject.

The outcome of all adverse events, non-serious and serious, was indicated as follows:

1: Recovered
2: Recovered with sequelae
3: Ongoing at subject study conclusion
4: Died

5: Unknown

Parents/guardians were informed about symptoms consistent with intussusception namely severe colicky pain, persistent vomiting, bloody stools, black stools, abdominal bloating and fever up to 41°C and made aware that there could be possible increased risk of intussusception after vaccination. Parents/guardians of the subjects were asked to contact the investigator if they noticed any signs and symptoms indicative of intussusception. The investigator and his staff were aware of the possible increased risk of intussusception and were to consider this diagnosis among children presenting these symptoms. If any cases of intussusception occurred during the study, the subjects were to be followed until the event had subsided. Clinical investigations were to be performed on any cases of intussusception that occurred to understand the occurrence of this rare event. Radiographic evidence of intussusception was to be obtained. The investigator was to take appropriate actions to treat the condition.

3.11.1 Pregnancy

Not applicable.

3.11.2 Prior and concomitant medication

At each study visit/contact, the investigator questioned the parents/guardians about any medication given to the subject.

Any immunosuppressants or other immune-modifying drugs or treatments, any vaccine other than the study vaccine(s) and any antipyretics administered at any time during the period starting 30 days prior to the first dose of study vaccine(s) and ending one month (minimum 30 days) after the last dose of study vaccine/placebo were recorded in the CRF with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment. Any antibiotics administered within 7 days preceding each study vaccine/placebo administration and during the first 7 days after each study vaccine/placebo administration were also recorded in the CRF with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment.

Any other concomitant medication administered prophylactically in anticipation of reaction to the vaccination were also recorded in the CRF with trade name and/or generic name of the medication, total daily dose, route of administration, start and end dates of treatment and coded as ‘Prophylactic’.

3.12 Assessment of immunogenicity variables

3.12.1 Intervals between study visits

To adequately assess the immune responses elicited by the vaccines, time intervals to be respected between visits for vaccination and blood sampling were detailed in the protocol (see Table 5).

*Table 5: Intervals between study visits**

Interval	Size of interval
Visit 1→Visit 2	49 – 69 days
Visit 2→Visit 3	30 – 42 days

Comments: * = Date of the previous visit was the reference date.

The protocol-specified intervals were adapted prior to analysis (see Table 6), and subjects with intervals outside the adapted intervals were excluded from the According to Protocol (ATP) immunogenicity cohort.

*Table 6: Adapted intervals between study visits**

Interval	Size of interval
Visit 1→Visit 2	49 – 83 days
Visit 2→Visit 3	21 – 48 days

Comments: * = Date of the previous visit was the reference date.

Supplement 1 presents deviations from the specified intervals.

Visit 4 took place at the end of the first RV season. No subjects were eliminated from the ATP cohort for immunogenicity for not respecting the time intervals between Visits 3 and 4.

3.12.2 Laboratory assays and timepoints

Whole blood samples (1 ml) were obtained at Visits 1, 3 and 4 from all subjects.

Blood samples were centrifuged and separated. All serum samples were stored at –20°C.

Serum anti-rotavirus IgA antibodies were measured by ELISA at the Laboratory of Dr. [redacted] Children's Hospital Medical Center, Cincinnati, USA and expressed in units per milliliter (U/ml). The assay cut-off was 20 U/ml. The ELISA test for anti-rotavirus antibodies uses the "sandwich principle". A solid phase enzyme-linked immunoassay technique is used to detect human anti-rotavirus IgA levels in serum. The assay used here was based on the assay described by Dr. R. Ward and his co-workers ([7]). The limit of detection of the assay was determined to be of 8.13 U/ml, whereas the limit of quantification (= the lowest concentration that could be reliably measured) was 12.34 U/ml. Therefore, the technical cut-off has been set at 20 U/ml as a theoretically and practically meaningful value.

A seronegative subject for anti-rotavirus IgA antibodies was defined as a subject who had antibody concentration below the assay cut-off value. A seropositive subject for anti-rotavirus IgA antibodies was defined as a subject who had antibody concentration greater than or equal to the assay cut-off value.

A subject negative for RV at pre-vaccination timepoint was defined as a subject who was seronegative for anti-rotavirus IgA antibodies at the pre-vaccination time point.

3.13 Data quality assurance

To ensure that study procedures conformed across all investigator sites, the protocol, CRF and safety reporting were reviewed with the investigator and his/her personnel responsible for the conduct of the study by the GSK Biologicals representative(s) at the investigator site prior to study start.

Adherence to the protocol requirements and verification of data generation accuracy was achieved through monitoring visits to each investigator site. Computer checks and blinded review of subject tabulations were performed to ensure consistency of CRF completion. All procedures were performed according to methodologies detailed in GSK Biologicals' Standard Operating Procedures.

3.14 Statistical methods

The analyses were performed using Statistical Analysis System (SAS) 8.2 and Proc StatXact-3 on Windows NT 4.0.

3.14.1 Primary endpoint

• Occurrence of RV GE during the period starting from 2 weeks after Dose 2 until the end of the first RV season following vaccination as detected by ELISA in stool samples.

3.14.2 Secondary endpoints

Efficacy endpoints
• Occurrence of RV GE during the period starting from 2 weeks after Dose 2 until the end of the first RV season following vaccination as detected by RT-PCR in stool samples.

• Occurrence of severe RV GE during the period starting from the end of the first RV season until the end of the second RV season following vaccination as detected by ELISA and as detected by RT-PCR in stool samples.

• Occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination as detected by ELISA and as detected by RT-PCR in stool samples.

• Occurrence of any and severe GE during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.

• Occurrence of asymptomatic RV infections during the period starting from 1 month after Dose 2 until the end of each RV season following vaccination.

• G type of the wild RV strain by RT-PCR.

Safety endpoints
• For each type of solicited symptom, occurrence of the symptom within the 15-day solicited follow-up period after each dose.

• Presence of RV antigen in any stool samples collected during the time starting from the day of Dose 1 and ending 2 weeks after Dose 2.

• Occurrence of unsolicited symptoms within 42 days after each dose, according to World Health Organization's (WHO) classification.

• Occurrence of serious adverse events throughout the entire study period.

Immunogenicity endpoints
• Anti-rotavirus IgA antibody concentrations before Dose 1, one month after Dose 2 and at the end of each RV season.

3.14.3 Determination of sample size

A total of 405 subjects were randomized to receive either the HRV vaccine or the placebo in a 2:1 ratio. Allowing for up to 10% of subjects who might not be evaluable for analyses of the primary objective, 360 subjects (240 in HRV and 120 in placebo groups respectively) were expected to be evaluable for the analysis of the primary objective. The assumption of 10% non-evaluable subjects was based on previous experience with similar trials in this population.

Assuming that in the placebo group the frequency of RV GE was 20% from two weeks after Dose 2 until the end of the first RV season following vaccination and that the efficacy rate would be 70%, the frequency of RV GE in the HRV group would be 6%. Therefore, 240 subjects in HRV group and 120 subjects in the placebo group would provide 95% power to detect a difference between the HRV group and the control group in the proportion of subjects with RV GE occurring from two weeks after Dose 2 until the end of the first RV season following vaccination (two-sided Fisher's exact test, alpha =0.05, when the proportions are 6% with HRV and 20% with placebo, Nquery).

The following table gives, for different assumptions, the power to detect a difference between the HRV group and the control group in the proportion of subjects with RV GE occurring from two weeks after Dose 2 until the end of the first RV season following vaccination (two-sided Fisher's exact test, alpha =0.05, with 240 subjects in HRV group and 120 subjects in the placebo group, Nquery):

% of subjects reporting RV GE in placebo group from two weeks after Dose 2 until the end of the first RV season following vaccination	% of subjects reporting RV GE in the HRV vaccine group from two weeks after Dose 2 until the end of the first RV season following vaccination	Efficacy %	Power %
18	5.4	70	92
15	4.5	70	86
20	5	75	97
20	7	65	91

3.14.4 Study cohorts/data sets analyzed

Four subject cohorts were evaluated:

Total cohort
The total cohort included all subjects enrolled in the study for whom data were available:

- Efficacy analysis based on the total cohort included all enrolled subjects for whom efficacy follow-up data was available. Efficacy follow-up was derived from any contact beyond 2 weeks after the second dose of HRV vaccine or placebo for the first efficacy follow-up period,
- Safety analysis based on the total cohort included all enrolled subjects for whom safety data were available,
- Immunogenicity analysis based on the total cohort included all enrolled subjects for whom immunogenicity data were available.

ATP cohort for safety

The ATP safety cohort included all subjects:

- who had received at least one dose of HRV vaccine or placebo according to the randomization list,
- with sufficient post-vaccination data to perform an analysis of safety (at least one documented dose),
- for whom the randomization code had not been broken by the investigator,
- who had not received a vaccine forbidden by or not specified in the protocol,
- who had received the vaccine or placebo dose according to protocol,
- who had not received a replacement vial,
- who were negative for serum anti-rotavirus IgA antibodies on the day of Dose 1.

ATP cohort for efficacy

The ATP efficacy cohort included all subjects from the ATP safety cohort:

- who received 2 doses of HRV vaccine or placebo according to the randomization list,
- who had no RV other than vaccine strain in stool samples collected between the day Dose 1 was administered and 2 weeks after Dose 2 of HRV vaccine or placebo was administered,
- who had entered into the surveillance period: had follow-up beyond 2 weeks after Dose 2 for the first efficacy follow-up period.

ATP cohort for immunogenicity

The ATP immunogenicity cohort included all subjects from the ATP safety cohort:

- who had not received medication forbidden by the protocol,
- whose underlying medical condition was not forbidden by the protocol,
- with no protocol violation of demographics (unknown age at study entry or outside protocol defined age-interval),
- who complied with vaccination schedule,
- who complied with blood sampling schedule,

- for whom immunogenicity data were available for IgA antibody concentration at pre and at one month post Dose 2 blood sampling time-points,
- who had no RV other than vaccine strain in stool samples collected from Dose 1 till Visit 3 (approximately one month after Dose 2),
- who had no concomitant infection unrelated to the vaccine which may influence the immune response.

The total cohort was used for the primary analysis of safety. The analysis on the ATP cohort for safety was planned to be performed only if more than 5% of the enrolled subjects were excluded from the ATP safety cohort.

The ATP efficacy cohort was used for the primary analysis of efficacy. An analysis of efficacy based on the total cohort was also performed.

The ATP immunogenicity cohort was used for the primary analysis of immunogenicity. An analysis of immunogenicity based on the total cohort was to be performed only if more than 5% of the enrolled subjects were excluded from the ATP immunogenicity cohort. In such a case, the total cohort analysis evaluated whether exclusion from the ATP cohort had biased the results.

Subjects excluded from the ATP cohorts were identified before data analysis after a review of the individual subject data blinded to group allocation.

The treatment assignment of each group was decoded for the analysis presented in this study report. Till the study end, access to the individual treatment decode will be strictly controlled and restricted to some GSK Biologicals' personnel. Only summary results are provided in this study report and individual subjects' numbers are not specified. The dissemination of the study results will be controlled.

Only statistical analyses pertaining to the final analysis performed at the end of the first RV season following vaccination are described below.

3.14.5 Analysis of demographics

Demographic characteristics (age in weeks, gender, race, weight and height) at Visit 1 were tabulated by group. This analysis was performed for subjects included in the ATP efficacy cohort, for subjects included in the ATP immunogenicity cohort, and for the total cohort.

3.14.6 Analysis of efficacy

The first efficacy follow-up period started from 2 weeks after Dose 2 and ended at the end of the first RV season on June 1, 2001.

Please refer to the glossary of terms for definition of an episode of RV GE. A global overview of the number of GE episode and RV GE episode reported by the subjects during the first efficacy follow-up period was provided for each group. The severity of all GE episodes reported during the first efficacy follow-up period was tabulated by group. A summary of RV GE episodes reported during the first efficacy follow-up period by type was provided.

The percentage of subjects reporting RV GE (any and severe intensity) during the first efficacy follow-up period was calculated by group with its 95% Confidence Interval (CI). Two-sided Fisher's exact test (significance level of α=0.05) was used to compare these percentages between groups.

The percentage of subjects hospitalized for GE during the first efficacy follow-up period was calculated by group with its 95% CI. Two-sided Fisher's exact test (significance level of α=0.05) was used to compare these percentages between groups.

Please refer to the glossary of terms for definition of an episode of asymptomatic RV infection. The percentage of subjects with asymptomatic RV infections between one month after Dose 2 and end of the first RV season following vaccination was calculated by group with its 95% CI. Two-sided Fisher's exact test (significance level of α=0.05) was used to compare these percentages between groups.

The efficacy rate (overall and by type) of the HRV vaccine relative to the placebo was calculated with its 95% CI against RV GE (any and severe intensity) occurring during the first efficacy follow-up period. The efficacy rate with its 95% CI was also calculated against hospitalization due to any GE and asymptomatic RV infection.

Vaccine efficacy was defined as the percent reduction in the frequency of the considered endpoint in vaccinated subjects compared with those subjects who received placebo.

The vaccine efficacy was calculated using the formula: $1 - RR = 1 - (ARV/ARU)$

RR = relative risk = ARV/ARU

- ARU = disease attack rate in unvaccinated population (estimated from the placebo group) = nu/Nu = number of subjects reporting at least one RV GE episode / total number of subjects in the control group.
- ARV = disease attack rate in vaccinated group = nv/Nv = number of subjects reporting at least one RV GE episode / total number of subjects in the HRV vaccine group.

The 95% CIs for vaccine efficacy were derived using a conditional to cases approach (refer to *Appendix B: Mathematical details about the computation of the 95%CI for vaccine efficacy*).

To check the robustness with respect to the statistical analysis, vaccine efficacy against the primary endpoint and its 95% CI was also estimated by the Mantel-Haenszel approach and by the Cox proportional-hazard model including the group effect as regressor. The Kaplan Meier survival curves were generated to analyze the time from 2 weeks after Dose 2 to the incidence of RV GE. The time was censored at the last contact in the first efficacy follow-up period.

In addition, person-year rates of RV GE (any and severe intensity), and of hospitalization due to any GE within each group were assessed using a loglinear Poisson model.

3.14.7 Analysis of safety

Solicited symptoms were recorded during the 15-day (Day 0 to Day 14) solicited follow-up period after each vaccination. Unsolicited symptoms were recorded during the 43-day (Day 0 to Day 42) follow-up period after each vaccination.

The percentages of doses and of subjects with any adverse experience (solicited or unsolicited) during the solicited follow-up period were computed by group, along with exact 95% CI. The same calculations were done for symptoms rated as grade “3” in intensity and for symptoms assessed as related to vaccination.

The percentages of doses and of subjects reporting specific solicited symptoms were calculated by group, with exact 95% CI, over the solicited follow-up period. The same calculations were done for solicited symptoms rated as grade “3” in intensity and for solicited symptoms assessed as related to vaccination.

The verbatim reports of unsolicited symptoms were coded by use of the WHO's Dictionary for Adverse Reaction Terminology; every verbatim term, as stated by the reporter, was matched to the appropriate WHO Preferred Term associated to the symptom. The percentage of subjects reporting unsolicited symptoms classified by WHO body system/WHO Preferred Terms within 43 days (Day 0 – Day 42) after any vaccination, with unsolicited symptoms rated as grade 3 in intensity and those assessed as related to vaccination were tabulated per group.

Differences between groups were explored using the two-sided Fisher's exact test on the following endpoints:

- percentage of subjects reporting at least one symptom (solicited or unsolicited) within 15 days (Day 0 – Day 14)) follow-up period after any dose,
- percentage of subjects reporting specific solicited symptoms (fever, fussiness/irritability, diarrhea, vomiting and loss of appetite) within 15 days (Day 0 –Day 14) follow-up period after any dose,
- percentage of subjects reporting unsolicited symptoms classified by WHO Preferred Terms during the 43 days (Day 0 – Day 42) follow-up period after any dose.

Statistically significant differences (p-value < 0.05) should be interpreted cautiously since, due to the number of endpoints, the differences observed in this study are likely to occur by chance alone.

The percentages of subjects with presence of RV in stool samples collected in case of diarrhea and/or vomiting from day of Dose 1 till 2 weeks after Dose 2 were tabulated.

The percentages of subjects who took at least one concomitant medication during the solicited follow-up period were tabulated per group.

The number of subjects reporting at least one SAE was presented per group.

3.14.8 Analysis of immunogenicity

GMCs (Geometric Mean Concentrations) and seropositivity rates to anti-rotavirus IgA antibodies were calculated with their 95% CI for each group, at each time point that blood samples were available. GMCs (expressed in U/ml) were computed by giving an arbitrary value of half the cut-off for non-detectable concentrations.

A subject who had seroconverted for anti-rotavirus IgA antibodies at a post-vaccination sampling timepoint was defined as a subject with appearance of anti-rotavirus IgA antibody concentration ≥ 20 U/ml in subjects initially (i.e. prior to

the first dose) negative for RV. The seroconversion rate was the seropositivity rate at the post-vaccination sampling timepoint in subjects initially negative for RV (for the ATP cohort, at post Dose 2 time point, seroconversion rate = seropositivity rate). The exact 95% CIs for difference in seroconversion rates one month after Dose 2 between vaccine and placebo groups were calculated.

The distribution of IgA antibody concentrations one month after Dose 2 were displayed using reverse cumulative curves.

The percentage of subjects reporting at least one RV GE episode during the first efficacy follow-up period by serological status for IgA antibody concentration one month after Dose 2 was computed.

3.15 Interim analysis

An unplanned interim analysis of the uncleaned efficacy data was performed after completion of Visit 4. The efficacy of the vaccine against RV GE (any and severe intensity) up to the end of the first RV season was computed and results were available in a descriptive summary form. The results of the interim analysis were kept in-house and no report was written. Individual decoding during this analysis was restricted to the statistician and the database administrator. The results of the unplanned interim analysis of the efficacy data were consistent with the results presented in this study report.

3.16 Annex analysis

Analysis of data from the end of the first year RV season post-vaccination until the end of the study (Visit 5) and efficacy analyses over both efficacy follow-up periods will be presented in an annex report.

3.17 Changes in conduct of the study/planned analyses

The following changes were made to the planned analyses:

In accordance with the report analysis plan (RAP) for the HRV vaccine project, the total cohort was used for the primary analysis of safety instead of the ATP cohort as specified in the study protocol.

In the protocol, it was planned that stool samples collected for any episode of GE occurring during the entire study period were to be analyzed by ELISA at Laboratory of Dr. [redacted] USA and by RT-PCR at the Laboratory of Prof. [redacted] Finland to detect RV. And if RV was detected in the stool specimens, the specimens were to be analyzed to determine the G type by RT-PCR at the Laboratory of Prof. [redacted] Finland. The following changes were made to the testing of stool samples collected during GE episodes:
1) One stool sample per GE episode (sample with higher volume) occurring after December 1, 2000 (from start of the RV season) was tested by RT-PCR at the Laboratory of Prof. [redacted] Finland irrespective of positive or negative ELISA result.

2) Stool samples collected in case of GE before December 1, 2000 (before start of the RV season) were tested only by ELISA and if positive, were tested by RT-PCR to identify the G type. A few stool samples collected before December 1, 2000 that were negative as detected by ELISA were mistakenly tested by RT-PCR and found positive. One subject with a stool sample collected before December 1, 2000 was found negative by ELISA and positive by RT-PCR and was therefore considered as having reported a RV GE in the efficacy calculation using RT-PCR method.

An unplanned interim analysis was performed. Refer to Section 3.15 for details.

Although it was not planned to score the GE episodes reported from day of Dose 1 till Day 14 (2 weeks) after Dose 2, the intensity of the GE episodes was calculated to standardize the data with future studies.

The 95% CIs for vaccine efficacy were derived according to the method described in the RAP for the HRV vaccine project and is presented in Appendix B, rather than using the Mantel-Haenszel approach as specified in the study protocol.

Seroconversion rate, vaccine efficacy against severe RV GE and against hospitalization due to any GE during the first efficacy period were calculated in accordance with the RAP for the HRV vaccine project to standardize the data with future studies.

GMCs to anti-rotavirus IgA antibody on seropositive subjects were calculated to allow comparison to GMCs obtained in other studies.

Although it was planned that access to the individual treatment decode would be available only to the statistician, database administrator and medical writer until study end to maintain the double-blind, access to the treatment code for some subjects was made available to the GSK Biologicals' Clinical Team prior to study end. This was because efficacy analysis of the first RV season revealed that subjects who had seroconverted were better protected against the natural infection than those who had not. In order to completely analyze the possible correlation between immunological markers and clinical efficacy seen during this pilot phase II efficacy study, access to the treatment code for subjects with RV GE (ELISA / RT-PCR positive) during the first RV season was given to the Clinical Development Manager and Director prior to study end.

4 Study Population

4.1 Study dates

The study began on August 21, 2000 (first subject, first visit). The data lock point for this final analysis was July 11, 2001 (the day Visit 4 was performed for all subjects).

In the mean time all subjects have completed Visit 5 at the end of the second RV season and the study has been completed.

4.2 Subject eligibility and attrition from study

4.2.1 Number and distribution of subjects

As planned, 405 subjects were enrolled in the study after checking of inclusion/exclusion criteria. The number of subjects at each study site is presented in Table 7.

Table 7: The number of subjects enrolled at each site by group (total cohort)

Site	HRV	Placebo	Total	
	n	n	n	%
[redacted]	34	17	51	12.6
	54	27	81	20.0
	82	41	123	30.4
	38	19	57	14.1
	34	17	51	12.6
	28	14	42	10.4
All	270	135	405	100

Notes: n/% = number/ percentage of subjects enrolled at each study site for each group or in total
Site = GSK Biologicals assigned site number

4.2.2 Study completion and drop-out

Follow-up during the second RV season was ongoing at the data lock point of this analysis. Therefore, drop-outs until Visit 4 (data lock point for analysis at the end of the first efficacy follow-up period) were assessed. Thirty-three subjects dropped out of the study until Visit 4 for reasons detailed in Table 8. Supplement 2 presents the drop-outs by visit.

Table 8: Counts of subjects enrolled, completed, dropped out and reason for drop-out until Visit 4 (total cohort)

	Group		
	HRV	**Placebo**	**Total**
Number of subjects enrolled	270	135	405
Number of subjects completed	249	123	372
Number of subjects dropped-out	21	12	33
Reasons for drop-out:			
Serious adverse event	0	0	0
Non-serious adverse event	6	2	8
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	13	8	21
Migrated/moved from study area	1	1	2
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	1	1	2
Others	0	0	0

Notes: Enrolled = number of subjects who where entered in the study
Completed = number of subjects who completed study Visit 4
Dropped-out = number of subjects who did not return for study Visit 4

Of the eight subjects who failed to complete Visit 4 as a result of non-serious adverse events, five subjects had vaccination-related adverse events. Details of the non-serious adverse events that led to withdrawal are given below.

Non-serious adverse events assessed as related to vaccination that led to withdrawal:

- One subject was withdrawn post Dose 1 after experiencing diarrhea (grade 1), irritability (grade 1), loss of appetite (grade 1) and vomiting (grade 1) on Day 1 after Dose 1.
- One subject was withdrawn post Dose 2 after experiencing vomiting and diarrhea during the solicited follow-up period after each dose. After Dose 1, diarrhea on Day 1 (grade 1), vomiting on Day 2 (grade 2), Day 3 (grade 1), Day 7 (grade 2) and on Day 12 (grade 2) were reported. After Dose 2, vomiting was reported on Day 1 (grade 1), Day 2 (grade 2), Day 3 (grade 1) and Day 4 (grade 3).
- One subject was withdrawn post Dose 1 after experiencing colicky stomachache (grade 3) for 16 days starting on Day 2 after Dose 1.
- One subject was withdrawn post Dose 1 after experiencing irritability on Day 0 (grade 1), Day 1 (grade 2), Day 2 (grade 3) and Day 3 (grade 2) after Dose 1 and also experiencing irritation of the anus (grade 3 and not related) for 3 days starting on Day 1 after Dose 1.
- One subject was withdrawn post Dose 1 after experiencing irritability on Day 0 (grade 2) and Day 1 (grade 2), and vomiting on Day 11 (grade 1) after Dose 1.

Non-serious adverse events assessed as not related to vaccination that led to withdrawal:

- One subject was withdrawn post Dose 1 because of blood in stools starting on Day 1 after Dose 1. The event was rated as grade 2 in intensity. During a visit to the outpatient clinic on Day 4, no *fissura ani* was found and the physician thought that the thermometer measurement may have caused a small wound to the rectum which may have resulted in presence of blood in stools. A stool sample was analysed on Day 4 at the hospital to detect blood and was negative. Blood test results were normal and stool culture was negative for *Clostridium difficile*, *Staphylococcus* and fungus. The parents were contacted by phone later and they reported that the blood in stools lasted for 28 days. No further stool samples were tested for presence of blood and the child was reported to be healthy.
- One subject was withdrawn post Dose 1 after experiencing two episodes of GE after Dose 1. The first episode began 16 days after Dose 1 (intensity grade 2) and lasted 34 days; RV was not detected in stool samples collected 1, 6 and 7 days after the start of the GE. The second GE episode began 57 days after Dose 1 (intensity grade 1) and lasted for 4 days; no stool samples were collected.
- One subject was withdrawn post Dose 1 after experiencing cough and sliminess for 9 days starting 5 days after Dose 1. Also, shortness of breath (dyspnea) was reported 9 days post Dose 1 and lasted for one day. All symptoms were rated as grade 2 in intensity.

4.2.3 Eligibility for analysis

Reasons for elimination from the ATP analyses are summarized in Table 9. See *Appendix A: Clintrial eligibility codes* for definitions of codes.

A total of 405 subjects were planned and enrolled in the study. Of these 14 subjects were eliminated from ATP safety cohort for the following reasons:

- Four subjects received DTP vaccination within 14 days of study vaccination which was forbidden by the protocol.
- Randomization failure occurred for three subjects since replacement vials (placebo) were used.
- One subject vomited 10 minutes after oral administration of the vaccine and may have not received the intended vaccine dose. This subject was therefore eliminated due to study vaccine not administered according to the protocol.
- The status for RV on the day of Dose 1 was not known for six subjects due to unavailable pre-vaccination blood sample, an invalid serology result or quantity not sufficient.

Of the 391 subjects included in the ATP safety cohort, 22 subjects who did not receive the second dose of the study vaccination and one subject who dropped-out before the start of the first efficacy follow-up period were eliminated from the ATP efficacy cohort.

Seventy of the 391 subjects included in the ATP safety cohort were eliminated from the ATP immunogenicity cohort for the following reasons:

- Three subjects received antibiotics within 7 days after Dose 2 and were therefore eliminated due to administration of medication forbidden by the protocol.
- Eleven subjects were eliminated due to non-compliance with vaccination schedule since they received Dose 2 outside of the adapted interval of 49 – 83 days between vaccinations.
- Nine subjects were eliminated due to non compliance with blood sampling schedule since their one month post Dose 2 blood sample was drawn outside of the adapted interval of 21 – 48 days between Dose 2 and the post-vaccination blood sampling visit.
- The one month post Dose 2 blood sample was not available for 47 subjects and they were therefore eliminated due to essential serological data missing.

Table 9: Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses with reasons for exclusion

	Total	Percent	HRV	Placebo
Number of subjects planned	**405**		**270**	**135**
Number of subjects enrolled (total cohort)	**405**	**100**	**270**	**135**
Administration of vaccine(s) in time window forbidden in the protocol (code 1040)	4		4	
Randomization failure (code 1050)	3		2	1
Study vaccine dose not administered according to protocol (code 1070)	1		1	
Initially positive or unknown status for RV on the day of Dose 1 (code 1500)	6		4	2
Number of subjects included in the ATP safety cohort	**391**	**96.5**	**259**	**132**
At least one study vaccine dose not administered (code 3010)	22		13	9
Subjects not entered into the surveillance period (code 3020)	1		1	
Number of subjects included in the ATP efficacy cohort - first efficacy follow-up period	**368**	**90.9**	**245**	**123**
Administration of any medication forbidden by the protocol (code 2040)	3		1	2
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	11		8	3
Non compliance with blood sampling schedule (including wrong and unknown date) (code 2090)	9		7	2
Essential serological data missing (code 2100)	47		34	13
Number of subjects included in the ATP immunogenicity cohort	**321**	**79.3**	**209**	**112**

Notes: Percent = percentage of subjects in the considered ATP cohort relative to the total cohort.
Comments: A subject may have more than one elimination code assigned for exclusion to a specific cohort. In that case, the lowest code number is listed in this table.
The ATP cohort for analysis of efficacy includes all enrolled subjects with no elimination codes beginning with one thousand or three thousand; the ATP cohort for analysis of immunogenicity includes all enrolled subjects with no elimination codes beginning with one or two thousand.

4.2.4 Compliance with protocol specified procedures

A total of 372 of the 405 enrolled subjects completed Visit 4. Therefore compliance with study completion until Visit 4 (end of the first RV season) was 91.9%.

For the total cohort, symptom sheets were completed for 520/526 doses (compliance for reactogenicity reporting 98.9%) in the HRV vaccine group and 257/261 doses (compliance for reactogenicity reporting 98.5%) in the placebo group. The compliance of documentation (symptom sheets) of the reactogenicity is presented in Supplement 3.

All subjects who did not respect the adapted intervals between vaccinations or for blood sampling were eliminated from the ATP immunogenicity analysis. Refer to Section 4.2.3.

For the ATP efficacy cohort, ELISA results for stool samples collected for GE episodes during the first efficacy follow-up period were not available for 7.1% episodes in the HRV vaccine group and 5.1% episodes in the placebo group. RT-PCR analysis results were not available for 9.8% episodes in the HRV vaccine group and 6.8% episodes in the placebo group. Results were unavailable due to stool samples not collected, invalid test results or samples not tested.

4.3 Demographic characteristics

4.3.1 Subjects included in the ATP efficacy cohort

Demographic characteristics for the ATP efficacy cohort are summarized in Table 10.

The demographic profile of the two groups was comparable with respect to age, gender, race, height and weight.

Table 10: Summary of demographic characteristics (ATP efficacy cohort)

Characteristics	Parameters or Categories	HRV N = 245		Placebo N = 123		Total N = 368	
		Value or n	%	Value or n	%	Value or n	%
Age at the first dose (weeks)	Mean	8.3	-	8.2	-	8.2	-
	SD	1.70	-	1.64	-	1.70	-
	Median	8	-	8	-	8	-
	Minimum	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-
Gender	Male	131	53.5	62	50.4	193	52.4
	Female	114	46.5	61	49.6	175	47.6
Race	White	243	99.2	123	100.0	366	99.5
	Black	0	0.0	0	0.0	0	0.0
	Oriental	0	0.0	0	0.0	0	0.0
	Other	2	0.8	0	0.0	2	0.5
Height (cm)	Mean	58.6	-	58.6	-	58.6	-
	SD	2.46	-	2.09	-	2.30	-
	Median	58	-	58	-	58	-
Weight (kg)	Mean	5.6	-	5.5	-	5.5	-
	SD	0.74	-	0.72	-	0.70	-
	Median	5.6	-	5.5	-	5.5	-

Notes: N = total number of subjects by group or in total (sum of all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

4.3.2 Total cohort

Demographic characteristics for the total cohort are summarized in Supplement 4.

4.3.3 Subjects included in the ATP immunogenicity cohort

Demographic characteristics for the subjects included in the ATP immunogenicity cohort are summarized in Supplement 5.

5 Analysis of Efficacy

5.1 Data sets analyzed

Analysis of efficacy was performed on the ATP cohort (primary analysis) and the total cohort. See Section 3.14.4 for definition of cohorts identified for analyses and Section 4.2.3 for description of eligibility for analyses.

5.2 According to protocol analysis

5.2.1 Characterization of GE episodes reported during the first efficacy follow-up period

The first efficacy follow-up period started from 2 weeks after Dose 2 and ended at the end of the first RV season on June 1, 2001. The duration of follow-up was similar for the two groups: the mean duration was 0.462 years for the HRV vaccine group and the placebo group. Refer to Supplement 6 for duration of follow-up for the first efficacy period.

85 subjects in the HRV vaccine group reported a total of 112 GE episodes and 45 subjects in the placebo group reported 59 GE episodes. The percentages of subjects who reported any GE during the first efficacy follow-up period was similar between the two groups (34.7% in the HRV vaccine group and 36.6% in the placebo group). Refer to Supplement 7 presenting the number and percentage of subjects who reported any GE episode(s) and RV GE episodes during the first efficacy follow-up period.

The percentage of subjects reporting RV GE was lower in the HRV vaccine group (3.3%) as compared to the placebo group (10.6%) when ELISA was used for detection of RV. No subject in either group had more than one episode of RV GE. (Refer to Supplement 7).

Table 11 presents a summary of intensity of any GE episodes and RV GE episodes reported during the first efficacy follow-up period. Using ELISA, five (38.5%) episodes of RV GE in the placebo group were noted as severe whereas only one episode (12.5%) was noted as severe in the HRV vaccine group. The severe RV GE episode in the HRV vaccine group was reported in a subject who was negative for serum anti-rotavirus IgA at one month post Dose 2. It should be noted that this subject had not respected protocol-specified time intervals: the interval between vaccinations was 21 days (outside adapted interval of 49-83 days) and interval between Dose 2 and post Dose 2 blood sampling was 62 days (outside adapted interval of 21-48 days). The severe RV GE episode (scored as 11 points) occurred 142 days after Dose 2 and was attributed to the G1 strain. The subject was seropositive for RV at the end of the first RV season. In the five severe episodes in the placebo group, G1 RV was isolated in four cases and one episode was attributed to the G2 strain. (Refer to Supplement 11).

As seen in Table 11, RT-PCR detected rotaviruses in more stool samples collected during GE episodes than ELISA. The percentage of subjects reporting RV GE was 4.9% in the HRV vaccine group as compared to 9.8% in the placebo group when RT-PCR was used for detection of RV (Refer to Supplement 7). All RV GE episodes detected only by RT-PCR were rated as mild when scored according to the 20-point scoring system.

Table 11: Number of GE episodes and RV GE episodes reported during the first efficacy follow-up period, by severity (ATP efficacy cohort)

		HRV		Placebo	
Event	**Severity**	**n**	**%**	**n**	**%**
Any GE	Unknown	2	1.8	0	0.0
	Mild (1 – 6)	78	69.6	39	66.1
	Moderate (7 – 10)	27	24.1	12	20.3
	Severe (≥ 11)	5	4.5	8	13.6
	Any	112	100	59	100
RV GE by ELISA	Mild (1 – 6)	2	25.0	3	23.1
	Moderate (7 – 10)	5	62.5	5	38.5
	Severe (≥ 11)	1	12.5	5	38.5
	Any	8	100	13	100
RV GE by RT-PCR	Mild (1 – 6)	6	50.0	3	25.0
	Moderate (7 – 10)	5	41.7	4	33.3
	Severe (≥ 11)	1	8.3	5	41.7
	Any	12	100	12	100

Notes: n/% = number/percentage of the specified event reported in each group, by severity, among all specified events reported during the first efficacy follow-up period
Any = any specified symptom reported, regardless of severity

Table 12 presents the percentage of subjects reporting RV GE episodes during the first efficacy follow-up period by RV G type.

G1 strain was the predominant strain causing RV GE episodes in both groups during the first efficacy follow-up period. In addition to the G1 strain, G2 (one case rated as severe intensity) and G9 (one case rated as moderate intensity) strains were isolated in the placebo group.

RV G type could not be identified for two subjects (one subject in each group). For the subject from the placebo group, RV was detected by ELISA but RT-PCR was not performed. The subject in the HRV vaccine group had a positive result for RV by ELISA but the RT-PCR test result was negative.

Table 12: Percentage of subjects with RV GE episodes reported during the first efficacy follow-up period, by RV G type (ATP efficacy cohort)

	HRV N = 245		**Placebo N = 123**	
Type	**n**	**%**	**n**	**%**
ELISA				
Any	8	3.3	13	10.6
Unknown	1	0.4	1	0.8
G1	7	2.9	10	8.1
G2	0	0.0	1	0.8
G9	0	0.0	1	0.8
RT-PCR				
Any	12	4.9	12	9.8
G1	12	4.9	10	8.1
G2	0	0.0	1	0.8
G9	0	0.0	1	0.8

Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified type in each group Any = number of subjects reporting at least one RV GE episode, whatever the type

Supplement 8 presents the characteristics of RV GE episodes detected by ELISA. Supplement 9 presents the characteristics of RV GE episodes detected by RT-PCR. No episodes of RV GE reported in either group required hospitalization during the first efficacy follow-up period. No dehydration was noted for any RV GE episodes in the HRV vaccine group while 1–5% dehydration was reported for two episodes in the placebo group. Oral rehydration was given after one episode of RV GE in the HRV vaccine group and three episodes in the placebo group.

5.2.2 Vaccine efficacy against RV GE during the first efficacy follow-up period

5.2.2.1 Vaccine efficacy as measured by ELISA (primary endpoint)

Table 13 presents the efficacy of the vaccine against RV GE during the first efficacy follow-up period as measured by ELISA.

The vaccine efficacy against occurrence of RV GE as detected by ELISA during the first efficacy period was 69.1% (95% CI, 19.6 – 88.9). There was a statistically significant decrease in the percentage of subjects reporting RV GE (detected by ELISA) during the first efficacy follow-up period in the HRV vaccine group as compared to the placebo group (p = 0.007, two-sided Fisher's exact test) and thus the primary objective of the study was reached.

The vaccine efficacy against occurrence of severe (score ≥ 11 on intensity scale) RV GE detected by ELISA during the first efficacy follow-up period was 90.0% (95% CI, 10.3 – 99.8). A statistically significant decrease in the percentage of subjects reporting severe RV GE during the first efficacy follow-up period was detected in the HRV vaccine group as compared to the placebo group (p = 0.017, two-sided Fisher's exact test).

Table 13: Percentage of subjects reporting RV GE and efficacy of the vaccine as measured by ELISA during the first efficacy follow-up period (ATP efficacy cohort)

Group	N	n	T (year)	n / T value	95%CI		n / N rate	95%CI		Vaccine efficacy %	95%CI		p-value
Any RV GE													
HRV	245	8	112.1	0.071	0.036	0.143	3.3	1.4	6.3	69.1	19.6	88.9	0.007
Placebo	123	13	55.2	0.236	0.137	0.406	10.6	5.7	17.4				
Severe RV GE													
HRV	245	1	113.2	0.009	0.001	0.063	0.4	0.0	2.3	90.0	10.3	99.8	0.017
Placebo	123	5	56.0	0.089	0.037	0.214	4.1	1.3	9.2				

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode, in each group
n/N= percentage of subjects reporting at least one RV GE episode in each group
n/T= person-year rate of RV GE in each group
95%CI= 95%confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Different statistical methods were used to compute the vaccine efficacy against RV GE. The data presented herein are the results of a conditional to cases approach (refer to *Appendix B: Mathematical details about the computation of the 95%CI for vaccine efficacy*). Applying the Mantel-Haenszel approach and the

Cox proportional-hazard model (results not included in this report) led to similar estimation of vaccine efficacy as results presented in this section.

5.2.2.2 Vaccine efficacy as measured by RT-PCR (secondary endpoint)

Table 14 presents the efficacy of the vaccine against RV GE during the first efficacy follow-up period as measured by RT-PCR.

Table 14: Percentage of subjects reporting RV GE (any intensity) and efficacy of the vaccine as measured by RT-PCR during the first efficacy follow-up period (ATP efficacy cohort)

Group	N	n	T (year)	n / T value	95%CI		n / N rate	95%CI		Vaccine efficacy %	95%CI		p-value
Any RV GE													
HRV	245	12	110.5	0.109	0.062	0.191	4.9	2.6	8.4	49.8	-22.2	79.4	0.115
Placebo	123	12	55.3	0.217	0.123	0.382	9.8	5.1	16.4				
Severe RV GE													
HRV	245	1	113.2	0.009	0.001	0.063	0.4	0.0	2.3	90.0	10.3	99.8	0.017
Placebo	123	5	56.0	0.089	0.037	0.214	4.1	1.3	9.2				

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode, in each group
n/N= percentage of subjects reporting at least one RV GE episode in each group
n/T= person-year rate of RV GE in each group
95%CI= 95%confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

When using a more sensitive assay such as RT-PCR for detection of RV the vaccine efficacy was 49.8% (95% CI, -22.2 – 79.4). A statistically significant decrease in the percentage of subjects reporting RV GE during the first efficacy follow-up period was not detected in the HRV vaccine group as compared to the placebo group (p = 0.115, two-sided Fisher's exact test). The use of RT-PCR method for detection of RV appeared to influence the estimate of vaccine efficacy against any RV GE.

The vaccine efficacy against occurrence of severe (score ≥ 11 on intensity scale) RV GE detected by RT-PCR during the first efficacy follow-up period was 90.0% (95% CI, 10.3 – 99.8). A statistically significant decrease in the percentage of subjects reporting severe RV GE during the first efficacy follow-up period was detected in the HRV vaccine group as compared to the placebo group (p = 0.017, two-sided Fisher's exact test). The use of RT-PCR method for detection of RV did not appear to modify the estimate of vaccine efficacy against severe RV GE.

Supplement 10 and Supplement 11 respectively present the efficacy against any and severe RV GE by type. Due to low number of cases attributed to other types (one case each attributed to G2 and G9 strains), cross-protection data obtained are limited.

5.2.3 Efficacy against asymptomatic infection during the first efficacy follow-up period

Table 15 presents the efficacy of the vaccine against asymptomatic RV infection (refer to the glossary for definition) during the first efficacy follow-up period.

Apart from the subjects with symptomatic RV GE, one subject in the HRV vaccine group and nine subjects (by ELISA)/ten subjects (by RT-PCR) in the placebo group had serological evidence of an asymptomatic RV infection during the period starting from one month after Dose 2 until the end of the first RV season following vaccination as indicated by seroconversion or ≥ 4-fold rises of anti-RV antibody IgA concentration between one month post Dose 2 and end of the first RV season time point. A statistically significant decrease ($p < 0.001$, two-sided Fisher's exact test) in the percentage of subjects reporting asymptomatic RV infection from one month after Dose 2 until the end of the first RV season following vaccination was observed in the HRV vaccine group as compared to the placebo group. Vaccine efficacy against occurrence of asymptomatic RV infection during the first efficacy follow-up period was > 94% using either of the RV detection methods (ELISA or RT-PCR).

Table 15: Percentage of subjects reporting asymptomatic RV infection and efficacy of the vaccine during the first efficacy follow-up period (ATP efficacy cohort)

Group	N	n	%	95%CI		Vaccine efficacy %	95%CI		p-value
ELISA									
HRV	197	1	0.5	0.0	2.8	94.2	58.5	99.9	< 0.001
Placebo	102	9	8.8	4.1	16.1				
RT-PCR									
HRV	195	1	0.5	0.0	2.8	94.7	62.9	99.9	< 0.001
Placebo	103	10	9.7	4.8	17.1				

Notes: N = number of subjects included in each group with available anti-rotavirus IgA antibody concentrations at Visits 3 and 4 and who did not report a RV GE between Visits 3 and 4
n = number of subjects reporting asymptomatic RV infection in each group
% = percentage of subjects reporting asymptomatic RV infection in each group
95%CI = 95%confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

5.2.4 Vaccine efficacy against hospitalization due to any GE during the first efficacy follow-up period

Supplement 12 presents the efficacy against hospitalization due to any GE. One subject from the HRV vaccine group was hospitalized due to non-RV GE during the first efficacy follow-up period.

5.3 Analysis of total cohort

Efficacy data for the total cohort are presented in Supplement 13 to Supplement 24. No subject with RV GE was eliminated from ATP efficacy cohort. The results of the total cohort analysis were similar to those observed in the ATP cohort.

6 Analysis of Safety

6.1 Data sets analyzed

Analysis of safety was performed only on the total cohort since less than 5% of subjects were eliminated from the ATP safety cohort. See Section 3.14.4 for description of analyses cohorts and Section 4.2.3 for explanation of eligibility for analysis.

6.2 Total cohort analysis

Data concerning solicited and unsolicited signs and symptoms was reported following 522/526 (99.2%) doses in the HRV vaccine group and 257/261 (98.5%) doses in the placebo group.

Table 16 presents the exposure to vaccination by group and overall. All enrolled subjects received at least the first dose of either HRV vaccine or placebo. Of the 23 subjects who received only one dose, seven subjects were drop-outs due to adverse events. Refer to Section 4.2.2 for further details on these subjects.

Table 16: Number and percentage of subjects who received vaccine dose(s) (total cohort)

Total number of doses received	HRV (N = 270)		Placebo (N= 135)		Total (N = 405)	
	n	%	n	%	n	%
1	14	5.2	9	6.7	23	5.7
2	256	94.8	126	93.3	382	94.3
Any	270	100	135	100	405	100

Notes: N = number of subjects included in each group or in total (sum of all groups)
n/% = number/percentage of subjects receiving the specified total number of doses in each group or in total (sum of all groups)
Any = number and percentage of subjects receiving at least one dose

6.2.1 Overall incidence of symptoms

Table 17 presents the percentages of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15-day solicited follow-up period.

There was no apparent increase in the incidence of symptoms following subsequent doses in either group. Results of the two-sided Fisher's exact test showed that a statistically significant difference was not detected between the HRV vaccine and the placebo groups with respect to the percentage of subjects reporting at least one symptom (solicited or unsolicited) within the 15-day solicited follow-up period after any dose (p-value > 0.05, two-sided Fisher's exact test).

Table 17: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15-day solicited follow-up period (total cohort)

		Symptoms					
		N	**n**	**%**	**95% CI**		
					L.L.	**U.L.**	
Dose 1	HRV	267	197	73.8	68.1	79.0	
	Placebo	133	94	70.7	62.2	78.2	
Dose 2	HRV	255	190	74.5	68.7	79.7	
	Placebo	124	90	72.6	63.8	80.2	
Overall doses	HRV	522	387	74.1	70.2	77.8	
	Placebo	257	184	71.6	65.7	77.0	
Overall subjects	HRV	267	234	87.6	83.1	91.3	p-value = 0.281
	Placebo	133	111	83.5	76.0	89.3	

Notes: 95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit
Each dose:
N = number of documented doses, for the considered dose
(a documented dose is defined as a dose for which a symptom sheet was completed and/or an unsolicited symptom was reported)
n/% = number/percentage of documented doses leading to reporting of at least one symptom, for the considered dose
Overall/dose:
N = total number of documented doses
n/% = total number/percentage of documented doses leading to reporting of at least one symptom
Overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting at least one symptom
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 25 presents the percentage of doses and of subjects reporting symptoms (solicited or unsolicited) rated as grade 3 in intensity during the 15-day solicited follow-up period and Supplement 26 presents the percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15-day solicited follow-up period.

6.2.2 Solicited signs and symptoms

Table 18 and Table 19 present respectively the percentage of subjects and of doses reporting specific solicited symptoms including those graded "3" in intensity and those considered to be related to vaccination, during the 15-day solicited follow-up period for all doses.

Irritability was the most commonly reported solicited symptom and diarrhea was the least frequently reported solicited symptom. Grade 3 solicited symptoms were reported at a similar incidence in the two groups. The majority of solicited symptoms were determined by the investigators to be related to vaccination.

Results of the two-sided Fisher's exact test showed that statistically significant differences were not detected between the HRV vaccine and the placebo group with respect to the percentage of subjects reporting each solicited symptom within the 15-day solicited follow-up period, except for loss of appetite (p = 0. 046, two-sided Fisher's exact test). The result of this exploratory analysis should be interpreted cautiously since, due to the number of endpoints, the difference observed is likely to occur by chance alone.

Table 18: Percentage of subjects reporting each solicited symptom including those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after any dose (total cohort)

Symptoms		**HRV N = 265**				**Placebo N = 133**				
		n	**%**	**95% CI**		**n**	**%**	**95% CI**		
				L.L.	**U.L.**			**L.L.**	**U.L.**	**p-value**
Diarrhea	Total	30	11.3	7.8	15.8	8	6.0	2.6	11.5	0.105
	Grade 3	5	1.9	0.6	4.3	0	0.0	0.0	2.7	
	Related	25	9.4	6.2	13.6	5	3.8	1.2	8.6	
Fever	Total	85	32.1	26.5	38.1	33	24.8	17.7	33.0	0.163
	Grade 3	1	0.4	0.0	2.1	0	0.0	0.0	2.7	
	Related	52	19.6	15.0	24.9	17	12.8	7.6	19.7	
Fussiness/ Irritability	Total	204	77.0	71.4	81.9	95	71.4	63.0	78.9	0.269
	Grade 3	22	8.3	5.3	12.3	12	9.0	4.7	15.2	
	Related	163	61.5	55.4	67.4	74	55.6	46.8	64.2	
Loss of appetite	Total	103	38.9	33.0	45.0	38	28.6	21.1	37.0	0.046
	Grade 3	1	0.4	0.0	2.1	0	0.0	0.0	2.7	
	Related	74	27.9	22.6	33.7	25	18.8	12.5	26.5	
Vomiting	Total	34	12.8	9.1	17.5	14	10.5	5.9	17.0	0.625
	Grade 3	12	4.5	2.4	7.8	2	1.5	0.2	5.3	
	Related	27	10.2	6.8	14.5	11	8.3	4.2	14.3	

Notes: N = number of subjects with at least one solicited symptom sheet completed
n/% = number/percentage of subjects reporting the specified symptom
95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
Grade 3, related = see section 3.11 for assessment of safety variables
p-value = two-sided Fisher's exact test (significant level of α=0.05)
Comments: Fever = rectal temperature ≥38.0°C or oral temperature ≥37.5°C

Table 19: Percentage of doses reporting each solicited symptom including those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period for overall doses (total cohort)

Symptom		**All doses**							
		HRV N = 520				**Placebo N = 257**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				L.L.	**U.L.**			**L.L.**	**U.L.**
Diarrhea	Total	31	6.0	4.1	8.4	9	3.5	1.6	6.5
	Grade 3	5	1.0	0.3	2.2	0	0.0	0.0	1.4
	Related	26	5.0	3.3	7.2	6	2.3	0.9	5.0
Fever	Total	101	19.4	16.1	23.1	45	17.5	13.1	22.7
	Grade 3	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Related	61	11.7	9.1	14.8	21	8.2	5.1	12.2
Irritability	Total	313	60.2	55.8	64.4	146	56.8	50.5	63.0
	Grade 3	23	4.4	2.8	6.6	12	4.7	2.4	8.0
	Related	243	46.7	42.4	51.1	103	40.1	34.0	46.3
Loss of appetite	Total	124	23.8	20.2	27.7	47	18.3	13.8	23.6
	Grade 3	1	0.2	0.0	1.1	0	0.0	0.0	1.4
	Related	89	17.1	14.0	20.6	31	12.1	8.3	16.7
Vomiting	Total	39	7.5	5.4	10.1	17	6.6	3.9	10.4
	Grade 3	12	2.3	1.2	4.0	2	0.8	0.1	2.8
	Related	30	5.8	3.9	8.1	13	5.1	2.7	8.5

Notes: N = total number of solicited symptom sheets completed
n/% = total number/percentage of doses leading to reporting of the specified symptom
95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
Grade 3, related = see section 3.11 for assessment of safety variables
Comments: Fever = rectal temperature ≥38.0°C or oral temperature ≥37.5°C

Supplement 27 gives the breakdown of solicited symptoms after each dose. There was no apparent increase in incidence of solicited symptoms with subsequent doses, except for fever. There were more reports of fever after the 2nd dose in both groups: for the HRV vaccine group, 12.1% after Dose 1 *versus* 27.1% after Dose 2 and for the placebo group, 10.5% after Dose 1 *versus* 25.0% after Dose 2. It should be noted that Dose 2, administered two months after Dose 1, was given during the winter season, between mid-October and end of January. The observed higher incidence of fever after Dose 2 could be therefore explained by the higher incidence of common cold or other winter ailments. Reports of grade 3 fever were rare after either dose. There was only one report of grade 3 fever after Dose 2 in the HRV vaccine group while no subjects in the placebo group had grade 3 fever.

There was no specific day following either dose during which diarrhea, vomiting or fever peaked. Refer to Supplement 28, Supplement 29, Supplement 30, Supplement 31, Supplement 32 and Supplement 33 for the prevalence of diarrhea, vomiting and fever during the solicited follow-up period, by day.

Supplement 34, Supplement 35 and Supplement 36 respectively present duration (in days) of diarrhea, vomiting and fever during the solicited follow-up period. Values for mean duration of diarrhea, vomiting and fever during the 15-day solicited follow-up period after each dose were similar between the two groups, ranging from 1.5 to 3 days. All three symptoms lasted slightly longer after the 2nd dose in the HRV vaccine group compared to the 1st dose. In the placebo group, fever had a slightly longer duration after the 2nd dose while diarrhea and vomiting had a slightly shorter duration.

6.2.2.1 Simultaneous occurrence of fever, diarrhea and vomiting during the solicited follow-up period after each dose

The simultaneous occurrence of fever, diarrhea and vomiting during the solicited follow-up period after each dose was also assessed since these symptoms characterize the complete clinical picture of RV GE. No subjects had fever, diarrhea and vomiting simultaneously but seven subjects (6 in the HRV vaccine group and 1 in the placebo group) had both diarrhea and vomiting occurring within the 15-day solicited follow-up period. Supplement 37 presents the summary of solicited gastrointestinal symptoms (diarrhea and vomiting) for subjects who reported both diarrhea and vomiting during the 15-day solicited follow-up period.

One subject had diarrhea (on Days 0 to 3, not related to vaccination) and vomiting (on Days 1 and 2, related to vaccination) rated as grade 3 in intensity after Dose 1. A G1 type RV was detected by RT-PCR in stool samples collected during the GE episode; ELISA test was negative for RV.

6.2.2.2 Occurrence of GE from day of Dose 1 till Day 14 after Dose 2

For this analysis, different definitions of GE were used during the solicited follow-up period and outside the solicited follow-up period. During the solicited follow-up period, GE was defined as diarrhea and/or vomiting. Outside the solicited follow-up period, diarrhea, vomiting and/or GE reported as unsolicited adverse events (WHO preferred term codes 0205, 0228 and 0293) were considered.

Supplement 38, Supplement 39 and Supplement 40 present data on GE episodes reported from day of Dose 1 till Day 14 after Dose 2. During the period starting from day of Dose 1 till Day 14 after Dose 2, a total of 85 episodes of GE were reported by 64 subjects in the HRV vaccine group and 36 episodes were reported by 23 subjects in the placebo group. The percentages of subjects who reported any

GE during this period were similar following GSK Biologicals' HRV vaccine (24.0%) and placebo (17.3%).

As seen in Supplement 41, some subjects (3.4% by ELISA and 6.4% by RT-PCR) in the vaccine group reported mild to moderate RV GE during this period *versus* none in the placebo group. Supplement 42 and Supplement 43 present a summary of RV GE episodes as detected by ELISA and RT-PCR respectively. As seen in Supplement 43, G1 type RV was detected in all RV GE cases, and all cases positive by ELISA were also positive by RT-PCR. As the G1 virus was not sequenced to determine if it was vaccine or wild type G1 virus, at this stage it is not possible to conclude that all these cases were truly due to the vaccine virus. Supplement 44 presents the number of RV GE episodes from day of Dose 1 till Day 14 after Dose 2, by severity. Some data were not available for four episodes of GE and therefore the severity for these four episodes could not be computed exactly.

6.2.3 Unsolicited symptoms

A total of 190 (71.2%) subjects in the HRV vaccine group and 93 (69.9%) subjects in the placebo group reported at least one unsolicited symptom, from Day 0 to Day 42 after any vaccination. Refer to Supplement 45 presenting the percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms from Day 0 to Day 42 after any vaccination. Results of the two-sided Fisher's exact test showed that statistically significant differences were not detected between the HRV vaccine and the placebo groups with respect to the percentage of subjects reporting each unsolicited symptom classified by WHO preferred terms, from Day 0 to Day 42 after any vaccination.

Table 20 presents the percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from Day 0 to Day 42 after any vaccination. Table 21 presents the percentage of subjects with grade 3 unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination.

Table 20: The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV N = 267				Placebo N = 133			
				95% CI				95% CI	
		n	%	L.L.	U.L.	n	%	L.L.	U.L.
At least one symptom		40	15	10.9	19.8	14	10.5	5.9	17.0
Body as a whole general (1810)	Crying abnormal (1162)	1	0.4	0	2.1	2	1.5	0.2	5.3
	Fatigue (0724)	5	1.9	0.6	4.3	5	3.8	1.2	8.6
	Pain (0730)	1	0.4	0	2.1	0	0	0	2.7
Gastrointestinal system (600)	Abdominal pain (0268)	8	3.0	1.3	5.8	1	0.8	0	4.1
	Constipation (0204)	1	0.4	0	2.1	0	0	0	2.7
	Flatulence (0285)	10	3.7	1.8	6.8	1	0.8	0	4.1
	Gastroesophageal reflux (1149)	15	5.6	3.2	9.1	3	2.3	0.5	6.5
Metabolic and nutritional (800)	Growth retarded (0379)	0	0	0	1.4	1	0.8	0	4.1
Neonatal and infancy (1600)	Feeding disorder neonatal (0909)	1	0.4	0	2.1	0	0	0	2.7
Platelet bleeding and clotting (1230)	Purpura (0459)	1	0.4	0	2.1	0	0	0	2.7
Psychiatric (500)	Insomnia (0183)	2	0.7	0.1	2.7	2	1.5	0.2	5.3
	Sleep disorder (0195)	1	0.4	0	2.1	1	0.8	0	4.1
	Somnolence (0197)	2	0.7	0.1	2.7	1	0.8	0	4.1
Skin and appendages (100)	Bullous eruption (0871)	0	0	0	1.4	1	0.8	0	4.1

Notes: N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting at least once the specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom assessed as related to vaccination, whatever the WHO Preferred terms
95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit

Table 21: The percentage of subjects with grade 3 unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV N = 267				Placebo N = 133			
				95% CI				95% CI	
		n	%	L.L.	U.L.	n	%	L.L.	U.L.
At least one symptom		17	6.4	3.8	10.0	13	9.8	5.3	16.1
Body as a whole general (1810)	Crying abnormal (1162)	1	0.4	0	2.1	3	2.3	0.5	6.5
	Fatigue (0724)	0	0	0	1.4	1	0.8	0	4.1
	Fever (0725)	3	1.1	0.2	3.2	1	0.8	0	4.1
	Injury (9001)	0	0	0	1.4	1	0.8	0	4.1
Gastrointestinal system (600)	Abdominal pain (0268)	1	0.4	0	2.1	1	0.8	0	4.1
	Flatulence (0285)	4	1.5	0.4	3.8	0	0	0	2.7
	Gastroesophageal reflux (1149)	1	0.4	0	2.1	0	0	0	2.7
	Melena (0306)	0	0	0	1.4	1	0.8	0	4.1
Psychiatric (500)	Insomnia (0183)	1	0.4	0	2.1	0	0	0	2.7
	Nervousness (0188)	2	0.7	0.1	2.7	0	0	0	2.7
Resistance mechanism (1830)	Infection viral (0740)	1	0.4	0	2.1	0	0	0	2.7
	Otitis media (0750)	1	0.4	0	2.1	2	1.5	0.2	5.3
	Upper resp tract infection (0543)	3	1.1	0.2	3.2	2	1.5	0.2	5.3
Respiratory system(1100)	Coughing (0513)	2	0.7	0.1	2.7	2	1.5	0.2	5.3
	Laryngitis (0521)	0	0	0	1.4	1	0.8	0	4.1
	Pneumonia (0528)	1	0.4	0	2.1	0	0	0	2.7
	Rhinitis (0539)	4	1.5	0.4	3.8	1	0.8	0	4.1
Skin and appendages (100)	Eczema (0012)	0	0	0	1.4	1	0.8	0	4.1
	Seborrhea (0033)	0	0	0	1.4	1	0.8	0	4.1
	Skin disorder (0037)	0	0	0	1.4	1	0.8	0	4.1
Vision (431)	Conjunctivitis (0238)	1	0.4	0	2.1	0	0	0	2.7

Notes: N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting at least once the specified unsolicited symptom
At least one symptom = number of subjects reporting at least one grade 3 unsolicited symptom, whatever the WHO Preferred terms
95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit

Supplement 46, Supplement 47 and Supplement 48 respectively present percentage of doses with related, grade 3 and all unsolicited symptoms from Day 0 to Day 42 after any vaccination.

Table 22 presents a summary of the unsolicited symptoms rated as grade 3 in intensity and assessed as related to vaccination, from Day 0 to Day 42 after any vaccination.

Table 22: Summary of unsolicited symptoms rated as grade 3 in intensity and assessed as related to vaccination from Day 0 to Day 42 after any vaccination (total cohort)

WHO Preferred term (CODE)	Onset	Duration
Abdominal pain (0268) Abdominal pain (0268) and crying abnormal (1162)	Day 2 post Dose 1 Day 6 post Dose 1	16 days 11 days
Flatulence (0285)	Day 5 post Dose 1	6 days
Flatulence (0285)	Day 5 post Dose 1	1 day
Flatulence (0285)	Day 0 post Dose 1	9 days
Fatigue (0724)	Day 0 post Dose 2	2 days
Gastroesophageal reflux (1149)	Day 4 post Dose 2	1 day

Supplement 49 and Supplement 50 present the percentage of subjects and doses respectively reporting gastrointestinal symptoms (WHO code 600) including those graded "3" in intensity and those considered to be related to vaccination, from Day 0 to Day 42 after any vaccination. Gastrointestinal symptoms tended to be reported more frequently in the HRV vaccine group as compared to the placebo group.

6.2.4 Concomitant medications/vaccinations

Table 23 presents the number and percentage of subjects who took at least one concomitant medication from Day 0 to Day 14 after each vaccination, by type. Supplement 51 and Supplement 52 present the percentage of subjects who took antipyretic by day, from Day 0 to Day 42, respectively after Dose 1 and Dose 2.

In total, 256 subjects [171 (63.3%) in the HRV vaccine group and 85 (63.0%) in the placebo group] started taking a medication after Visit 1 (with start date between the day of Dose 1 and Visit 4).

The percentage of subjects who received medication during the solicited follow-up period was similar between the HRV vaccine and the placebo groups. One subject in the HRV vaccine group received prophylactic antipyretic medication during the solicited follow-up period after Dose 1. This subject had experienced irritability on Days 1, 2 (grade 2) and 3 (grade 1) after the first dose.

Table 23: Number and percentage of subjects who took at least one concomitant medication from Day 0 to Day 14 after each vaccination, by type (total cohort)

Type of medication	Dose 1							
	HRV N = 270				Placebo N = 135			
	n	%	95% CI		n	%	95% CI	
			L.L.	UL			L.L.	U.L.
Any medication	39	14.4	10.5	19.2	15	11.1	6.4	17.7
Any antipyretics	11	4.1	2.1	7.2	4	3.0	0.8	7.4
Prophylactic antipyretics	1	0.4	0.0	2.0	0	0.0	0.0	2.7
Any antibiotics	11	4.1	2.1	7.2	7	5.2	2.1	10.4

Notes: N = number of subjects who received the considered dose
n/% = number/percentage of subjects who started taking the specified concomitant medication at least once from Day 0 to Day 14 after vaccination
95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit

Table 23 (continued): Number and percentage of subjects who took at least one concomitant medication from Day 0 to Day 14 after each vaccination, by type (total cohort)

Type of medication	Dose 2							
	HRV N = 256				Placebo N = 126			
	n	%	95% CI		n	%	95% CI	
			L.L.	U.L.			L.L.	U.L.
Any medication	48	18.8	14.2	24.1	31	24.6	17.4	33.1
Any antipyretics	29	11.3	7.7	15.9	23	18.3	11.9	26.1
Prophylactic antipyretics	0	0.0	0.0	1.4	0	0.0	0.0	2.9
Any antibiotics	6	2.3	0.9	5.0	8	6.3	2.8	12.1

Notes: N = number of subjects who received the considered dose
n/% = number/percentage of subjects who started taking the specified concomitant medication at least once from Day 0 to Day 14 after vaccination
95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit

6.2.5 Serious Adverse Events

Case narratives and the summary table for the SAEs reported up to Visit 4 are appended to the study report.

Nineteen subjects (15 in the HRV vaccine group and 4 in the placebo group) reported at least one SAE during the study up to Visit 4. None of the SAEs were assessed as related to study vaccination.

7 Analysis of Immunogenicity

7.1 Data sets analyzed

Analysis of immunogenicity was performed on the ATP cohort (primary analysis) and the total cohort. See Section 3.14.4 for definition of cohorts identified for analyses and Section 4.2.3 for description of eligibility for analyses.

7.2 According to protocol analysis

7.2.1 Anti- rotavirus IgA antibody response

Anti-rotavirus IgA antibody GMCs and seropositivity rates at each sampling timepoint are presented in Table 24. Distribution of anti-rotavirus IgA antibody concentrations is presented in Supplement 53. Supplement 54 presents reverse cumulative distribution curves of anti-rotavirus IgA antibody concentrations in the HRV vaccine group one month after Dose 2.

One month after the second dose, 80.4% of subjects in the HRV vaccine group and none in the placebo group had seroconverted as tested by ELISA. Anti-rotavirus IgA antibody GMCs had increased substantially in the HRV vaccine group one month after the second dose. At the end of the first RV season, 75.7% of the subjects in the HRV vaccine group had concentrations of anti-rotavirus IgA antibodies above the cut-off value (20 U/ml) while 15.1% of the placebo recipients had seroconverted.

Table 24: Anti-rotavirus IgA antibody GMCs and seropositivity rates by ELISA (ATP immunogenicity cohort)

			≥ 20 U/ml				GMC (U/ml)				
					95% CI			95% CI			
Group	**Timing**	**N**	**n**	**%**	**L.L.**	**U.L.**	**Value**	**L.L.**	**U.L.**	**Min**	**Max**
HRV	Pre	209	0	0.0	0.0	1.7	<20	-	-	<20	<20
	PII(M3)	209	168	80.4	74.3	85.5	164.0	129.7	207.3	<20	4161
	ES1	189	143	75.7	68.9	81.6	83.2	67.2	103.0	<20	3211
Placebo	Pre	112	0	0.0	0.0	3.2	<20	-	-	<20	<20
	PII(M3)	112	0	0.0	0.0	3.2	<20	-	-	<20	<20
	ES1	106	16	15.1	8.9	23.4	<20	-	-	<20	1101

Notes: N= number of subjects with available data
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval
Min = Minimum concentration
Max = Maximum concentration
L.L. = lower limit, U.L. = upper limit
Pre = Pre-vaccination
PII(M3) = one month after the second vaccination
ES1 = end of the first RV season

In order to compare antibody concentrations induced by the vaccine across studies and also to compare with antibody concentrations induced by the natural RV infection, anti-rotavirus IgA GMCs were calculated on the subjects who had seroconverted after vaccination or natural infection. The anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies are presented in Table 25. Results show that the GMCs induced by the vaccine are lower than the GMCs induced by the natural infection.

Table 25: Anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies (ATP immunogenicity cohort)

			GMC (U/ml)				
				95% CI		Range	
Group	**Timing**	**N**	**Value**	**L.L.**	**U.L.**	**Min**	**Max**
HRV	PII(M3)	168	324.6	273.0	385.9	30	4161
	ES1	143	164.5	139.4	194.1	27	3211
Placebo	ES1	16	573.9	407.6	808.0	116	1101

Notes: N= number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval
Min = Minimum concentration, Max = Maximum concentration
L.L. = lower limit, U.L. = upper limit
PII(M3) = one month after the second vaccination
ES1 = end of the first RV season

Table 26 presents the exact 95% CIs for the difference in seroconversion rate one month after Dose 2 between HRV vaccine and placebo groups. The lower limit of the exact 95% CIs for the difference in seroconversion rate one month after Dose 2 between vaccine and placebo groups was 73.5%, indicating that the seroconversion rate was significantly higher in the HRV vaccine group as compared to the placebo group

Table 26: Difference in percentage of subjects who seroconverted for serum anti-rotavirus IgA antibody one month after Dose 2 between HRV vaccine and placebo groups (ATP immunogenicity cohort)

HRV		Placebo		Difference in seroconversion rates HRV minus Placebo		
				Value	95% CI	
N	%	N	%	%	L.L.	U.L.
209	80.4	112	0.0	80.4	73.5	86.3

Notes: N = number of subjects with available data
% = percentage of subjects who seroconverted one month after Dose 2
95% CI = exact 95% confidence interval
L.L. = lower limit, U.L. = upper limit

Although no correlate of protection against RV infection and disease has yet been identified, it is considered that anti-rotavirus IgA antibodies are a strong marker of protection ([8], [9]). Indeed, it was observed that subjects in the HRV vaccine group who had seroconverted at one month post Dose 2 of vaccine, were less likely to develop RV GE during the first efficacy follow-up period (Refer to Supplement 55). The single subject in the HRV vaccine group who developed a severe RV GE had not seroconverted one month after Dose 2. Details of the RV GE episodes as detected by ELISA and RT-PCR and reported during the first efficacy follow-up period in subjects in the HRV vaccine group who had seroconverted after Dose 2 are given in Table 27.

Table 27: Details of the RV GE episodes reported during the first efficacy follow-up period in subjects in the HRV vaccine group who had seroconverted one month after Dose 2(ATP efficacy cohort)

IgA antibody concentration at one month post Dose 2	G type of RV isolated	Severity score of the RV GE episode (intensity)
ELISA used for RV detection		
28 U/ml	Not determined*	6 (mild)
116 U/ml	G1	7 (moderate)
432 U/ml	G1	8 (moderate)
RT-PCR used for RV detection		
116 U/ml	G1	7 (moderate)
294 U/ml	G1	4 (mild)
409 U/ml	G1	6 (mild)
432 U/ml	G1	8 (moderate)
661 U/ml	G1	4 (mild)
3668 U/ml	G1	6 (mild)

Comments: *RT-PCR was negative

7.3 Analysis of total cohort

Immunogenicity data for the total cohort are presented in Supplement 56, Supplement 57 and Supplement 58. The results of this analysis are consistent with those observed in the ATP cohort.

8 Discussion

This final analysis provides data on the efficacy during the first RV season as well as reactogenicity, safety and immunogenicity following two doses of GSK Biologicals' HRV vaccine containing the strain RIX4414 at a virus concentration of $10^{4.7}$ ffu in infants (6 – 12 weeks old at study entry) previously uninfected with HRV.

At the end of the first RV season, this randomized, placebo-controlled, double-blind study conducted in Finland showed that two doses of $10^{4.7}$ ffu RIX4414 had 69.1% (95% CI, 19.6 – 88.9%) efficacy in decreasing the incidence of any RV GE (detected by ELISA) relative to the placebo. The protective efficacy rate was 90.0% (95% CI, 10.3 – 99.8%) against severe (≥ 11 points on a 20-point scale) RV GE. The RV type detected during the epidemic season was mainly G1. No other vaccine was administered concomitantly with the HRV vaccine.

In addition to the ELISA method that is routinely used for detection of rotaviruses, the more sensitive RT-PCR method ([5], [6], [10]) was also used for detection of RV in stool samples during GE episodes. As expected, more RV positive GE episodes were detected by RT-PCR. However, all cases that were detected only by RT-PCR were rated as mild in intensity indicating that there probably is a correlation between the amount of RV excreted and severity of the disease. The use of RT-PCR method did not affect the efficacy estimate against severe RV GE episodes but did influence the estimate of vaccine efficacy against any RV GE.

GSK Biologicals' HRV vaccine was safe and did not appear to be more reactogenic than the placebo. During the period from the day of Dose 1 until 2 weeks after Dose 2, mild to moderate episodes of RV GE were observed in 3.4 % of vaccinees *versus* 0% of placebo recipients.

One month after the 2nd dose, 80.4% of subjects in the HRV vaccine group had seroconverted as measured by IgA (ELISA) indicating that the HRV vaccine was immunogenic. These results were in accordance with results of an earlier study (444563/003) with GSK Biologicals' HRV vaccine conducted in the same age group in Finland.

As reported in the literature, two doses of the parent 89-12 vaccine candidate ($10^{5.0}$ pfu) had 89% vaccine efficacy (95% CI, 65.4-94.5%) against any symptomatic RV GE after the first RV season and the observed seroconversion rate was 90% ([2]). Comparing the results observed in this pilot study with historical data of the 89-12 vaccine candidate, some differences were apparent.

The protective efficacy of RIX4414 in terms of decreasing incidence of RV GE was similar to that of 89-12 for severe disease.

Reactogenicity after administration of RIX4414 was markedly low in terms of post-vaccination fever, diarrhea and vomiting as compared to 89-12. Also, the peak of fever observed on Day 3 after vaccination with 89-12 was not seen with RIX4414. The lower reactogenicity and immunogenicity observed with RIX4414 could indicate that RIX4414 strain is more attenuated than the parent strain. Several parameters could be contributing to the differences between RIX4414 and 89-12 strains: (i) the virus concentration of the antigen ($10^{4.7}$ ffu for RIX4414 versus $10^{5.0}$ ffu for 89-12), (ii) the further passages of RIX4414 on VERO cells as compared to 89-12, (iii) the younger age of infants in the RIX4414 study (mean age 8 weeks at first dose versus 12 weeks for the 89-12 study), and (iv) the different buffer used in the two studies (calcium carbonate buffer versus Mylanta® prior to vaccine ingestion with 89-12).

GSK Biologicals' HRV vaccine was efficacious, safe and immunogenic relative to the placebo and should be evaluated further in larger clinical trials. Results from this pilot efficacy trial and the previous dose-ranging (444563/003) study indicate that immunogenicity and protective efficacy of RIX4414 may be optimized with higher viral concentrations.

9 Overall Conclusions

- This pilot efficacy trial was designed to evaluate the efficacy of GSK Biologicals' HRV vaccine , strain RIX 4414 against RV GE. The efficacy of two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine in decreasing the incidence of RV GE as detected by ELISA relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first RV season following vaccination was demonstrated in healthy infants (6–12 weeks old at study entry) not previously infected with HRV. Thus, the primary objective of the study was met and the proof of concept in terms of clinical protection with a new HRV vaccine strain, RIX 4414, demonstrated.

- GSK Biologicals' HRV vaccine was efficacious in decreasing the incidence of severe RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first RV season following vaccination.

- GSK Biologicals' HRV vaccine was efficacious in decreasing the incidence of asymptomatic RV infections relative to the placebo during the period starting from one month after Dose 2 until the end of the first RV season following vaccination.

- The G1 type was predominant among the wild type RV circulating during the first RV season following vaccination.

- The method (ELISA *versus* RT-PCR) used for detection of RV appeared to influence the estimate of vaccine efficacy against any RV GE but not against severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the first RV season following vaccination.

- GSK Biologicals' HRV vaccine appeared safe when given as a two-dose regimen at a virus concentration of $10^{4.7}$ ffu to healthy infants at 2 and 4 months of age. The reactogenicity profile of the HRV vaccine was similar to that of the placebo in terms of the incidences of solicited and unsolicited symptoms reported after vaccination. No vaccination-related SAEs were reported.

- Gastrointestinal symptoms rated as mild or moderate in intensity were induced in a small proportion of vaccinees as indicated by the presence of RV in stool samples collected in case of GE during the period starting from the day of Dose 1 and ending 2 weeks after Dose 2.

- One month after the 2nd dose, 80.4% of subjects in the HRV vaccine group seroconverted indicating that the vaccine was immunogenic in terms of serum anti-rotavirus IgA antibodies.

10 References.

[1] Bernstein DI, Smith VE, Sherwood JR, Schiff GM, Sander DS, DeFeudis D, Spriggs DR, Ward RL. Safety and immunogenicity of a live attenuated human rotavirus 89-12 vaccine. Vaccine 1998;16:381-7.

[2] Bernstein DI, Sack DA, Rothstein E, Reisinger K, Smith VE, O'Sullivan D, Spriggs DR, Ward RL. Efficacy of live attenuated human rotavirus vaccine 89-12 in infants: a randomised placebo-controlled trial. Lancet 1999;354:287-90.

[3] Ruuska T and Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for severity of diarrheal episodes. Scand J Infect Dis 1990;22:259-267.

[4] Joensuu J, Koskenniemi E, Pang X-L, Vesikari Tl. Randomised placebo-controlled trial of dose rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis. Lancet 1997;350:1205-9.

[5] Xu L, Harbour D, McCrae MA. The application of polymerase chain reaction to the detection of rotaviruses in faeces. J Virol Method 1990;27:29-38.

[6] Pang X-L, Joensuu J, Hoshino Y, Kapikan AZ, Vesikari T. Rotaviruses detected by reverse transcription polymerase chain reaction in acute gastroenteritis during a trial of rhesus-human reassortant rotavirus tetravalent vaccine: implication s of vaccine efficacy analysis.

[7] Ward RL, Bernstein DI, Shukla R, *et al*. Effects of antibody to Rotavirus on protection of adults challenged with a human Rotavirus. J. Infect. Dis. 1989; 159:79-88.

[8] Ward RL. Mechanisms of protection against rotavirus in humans and mice. J Infect Dis 1996; 174 (Suppl 1);S51-8.

[9] Velaquez FR, Matson DO, Guerrero ML et al. Serum antibody as a marker of protection against natural rotavirus infection and disease. J Infect Dis 2000;182.

[10] Wilde J, Eiden J, Willoughby J. Improved detection of rotavirus shedding by polymerase chain reaction. Lancet 1991;337:323-6.

11 Supplements

Supplement 1: Deviations from specifications for age and intervals between study visits (total cohort)

Group	**Age**		**VC1–VC2**		**VC2–BS2**	
	Protocol	**Adapted**	**Protocol**	**Adapted**	**Protocol**	**Adapted**
	from 6 to 12 weeks	**from 6 to 12 weeks**	**from 49 to 69 days**	**from 49 to 83 days**	**from 30 to 42 days**	**from 21 to 48 days**
HRV	/	/	n = 16 subjects (from -28 to 49 days) 6.3% of 256 (14 subjects with empty value)	n = 8 subjects (from -28 to 35 days) 3.1% of 256 (14 subjects with empty value)	n = 15 subjects (from -3 to 27 days) 6.1% of 245 (25 subjects with empty value)	n = 9 subjects (from 1 to 21 days) 3.7% of 245 (25 subjects with empty value)
Placebo	/	/	n = 5 subjects (from -2 to 27 days) 4.0% of 126 (9 subjects with empty value)	n = 3 subjects (from -2 to 13 days) 2.4% of 126 (9 subjects with empty value)	n = 7 subjects (from 1 to 34 days) 5.7% of 122 (13 subjects with empty value)	n = 2 subjects (from 4 to 28 days) 1.6% of 122 (13 subjects with empty value)

Notes: VC1 visit for first dose VC2 visit for second dose
BS2 = blood sample one month after Dose 2
n = number of subjects out of the specified range of age or of the considered interval
% (for interval between visits) = percentage of subjects out of the specified interval among subjects present at the considered visits.

Supplement 2: Number of subjects at each visit and list of dropped-out subjects (total cohort)

	Visit 1	Pid	Date of last contact	Visit 2	Pid	Date of last contact	Visit 3	Pid	Date of last contact	Visit 4
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.										

Notes: Pid = subject identification of a drop-out N° = dropped-out subject number between the two considered visits

Supplement 3: Compliance (total cohort)

Dose	Group	Number of Doses	Doses NOT according to protocol	Number of general SS	Compliance % general
1	HRV	270	0	265	98.1
	Placebo	135	0	133	98.5
2	HRV	256	1	255	99.6
	Placebo	126	0	124	98.4
Total	HRV	526	1	520	98.9
	Placebo	261	0	257	98.5

Notes: SS = symptom sheet

Supplement 4: Summary of demographic characteristics (total cohort)

Characteristics	Parameters or Categories	HRV N= 270		Placebo N= 135		Total N= 405	
		Value or n	%	Value or n	%	Value or n	%
Age at the first dose (weeks)	Mean	8.3	-	8.3	-	8.3	-
	SD	1.69	-	1.65	-	1.70	-
	Median	8	-	8	-	8	-
	Minimum	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-
Gender	Male	146	54.1	68	50.4	214	52.8
	Female	124	45.9	67	49.6	191	47.2
Race	White	267	98.9	134	99.3	401	99.0
	Black	0	0.0	0	0.0	0	0.0
	Oriental	1	0.4	0	0.0	1	0.2
	Other	2	0.7	1	0.7	3	0.7
Height (cm)	Mean	58.7	-	58.6	-	58.6	-
	SD	2.52	-	2.20	-	2.40	-
	Median	58	-	58	-	58	-
Weight (kg)	Mean	5.6	-	5.5	-	5.5	-
	SD	0.76	-	0.77	-	0.80	-
	Median	5.6	-	5.5	-	5.5	-

Notes: N = total number of subjects by group or in total (sum of all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Supplement 5: Summary of demographic characteristics (ATP immunogenicity cohort)

Characteristics	Parameters or Categories	HRV N= 209		Placebo N= 112		Total N= 321	
		Value or n	%	Value or n	%	Value or n	%
Age at the first dose (weeks)	Mean	8.3	-	8.3	-	8.3	-
	SD	1.70	-	1.64	-	1.70	-
	Median	8	-	8	-	8	-
	Minimum	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-
Gender	Male	112	53.6	55	49.1	167	52.0
	Female	97	46.4	57	50.9	154	48.0
Race	White	207	99.0	112	100.0	319	99.4
	Black	0	0.0	0	0.0	0	0.0
	Oriental	0	0.0	0	0.0	0	0.0
	Other	2	1.0	0	0.0	2	0.6
Height (cm)	Mean	58.7	-	58.6	-	58.7	-
	SD	2.50	-	2.10	-	2.40	-
	Median	58	-	58	-	58	-
Weight (kg)	Mean	5.6	-	5.5	-	5.5	-
	SD	0.74	-	0.70	-	0.70	-
	Median	5.6	-	5.5	-	5.5	-

Notes: N = total number of subjects by group or in total (sum of all s)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD= standard deviation

Supplement 6: Duration (in years) of the follow-up periods for the first efficacy period (ATP efficacy cohort)

Duration (years) of follow-up period	**HRV**	**Placebo**
N	245	123
Total	113.2	56.9
Mean	0.462	0.462
Minimum	0.016	0.121
Q1	0.422	0.422
Median	0.468	0.468
Q3	0.510	0.521
Maximum	0.595	0.584

Notes: N = number of subjects included in each group
Total = sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 7: Number and percentage of subjects who reported GE episode(s) during the first efficacy follow-up period (ATP efficacy cohort)

Event	**Total number of episodes reported**	**HRV N = 245**		**Placebo N = 123**	
		n	**%**	**n**	**%**
GE	1	62	25.3	35	28.5
	2	19	7.8	6	4.9
	3	4	1.6	4	3.3
	Any	85	34.7	45	36.6
Rotavirus GE ELISA	1	8	3.3	13	10.6
	Any	8	3.3	13	10.6
RT-PCR	1	12	4.9	12	9.8
	Any	12	4.9	12	9.8

Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified symptom = sum of the "Total number of episode reported"

Supplement 8: Characteristics of RV GE episodes reported during the first efficacy follow-up period, by ELISA (ATP efficacy cohort)

Characteristics	Parameters or categories	HRV N = 245 Value or n	%	Placebo N = 123 Value or n	%
	N'	8	-	13	-
Severity score	Mean	7.75	-	9.85	-
	SD	1.909	-	4.059	-
	Median	7.5	-	8.0	-
	Minimum	5	-	5	-
	Maximum	11	-	17	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	7	87.5	9	69.2
	5	1	12.5	2	15.4
	≥ 6 days	0	0.0	2	15.4
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	1-3	6	75.0	2	15.4
	4-5	0	0.0	4	30.8
	≥ 6	2	25.0	7	53.8
Duration of vomiting	0 day	1	12.5	2	15.4
	1 day	2	25.0	5	38.5
	2 days	4	50.0	2	15.4
	≥ 3 days	1	12.5	4	30.8
Maximum number of episodes of vomiting/24 hours	0	1	12.5	2	15.4
	1	2	25.0	3	23.1
	2-4	4	50.0	4	30.8
	≥ 5	1	12.5	4	30.8
Maximum fever reported/24 hours (measured rectally)	< 37.1°C	0	0.0	0	0.0
	37.1-38.4°C	4	50.0	4	30.8
	38.5-38.9°C	2	25.0	4	30.8
	≥ 39°C	2	25.0	5	38.5
Treatment	none	7	87.5	10	76.9
	Rehydration	1	12.5	3	23.1
	Hospitalization	0	0.0	0	0.0
Dehydration	none	8	100	11	84.6
	1-5%	0	0.0	2	15.4
	≥ 6%	0	0.0	0	0.0

Notes: N = number of subjects included in each group
N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation

Supplement 9: Characteristics of RV GE episodes reported during first efficacy follow-up period, by RT-PCR (ATP efficacy cohort)

Characteristics	Parameters or categories	HRV N = 245 Value or n	%	Placebo N = 123 Value or n	%
	N'	12	-	12	-
Severity score	Mean	6.58	-	10.00	-
	SD	2.392	-	4.200	-
	Median	6.5	-	9.0	-
	Minimum	3	-	5	-
	Maximum	11	-	17	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	11	91.7	8	66.7
	5	1	8.3	2	16.7
	≥ 6 days	0	0.0	2	16.7
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	1-3	9	75.0	2	16.7
	4-5	1	8.3	3	25.0
	≥ 6	2	16.7	7	58.3
Duration of vomiting	0 day	4	33.3	2	16.7
	1 day	3	25.0	5	41.7
	2 days	4	33.3	1	8.3
	≥ 3 days	1	8.3	4	33.3
Maximum number of episodes of vomiting/24 hours	0	4	33.3	2	16.7
	1	2	16.7	3	25.0
	2-4	5	41.7	3	25.0
	≥ 5	1	8.3	4	33.3
Maximum fever reported/24 hours (measured rectally)	< 37.1°C	1	8.3	0	0.0
	37.1-38.4°C	5	41.7	3	25.0
	38.5-38.9°C	4	33.3	4	33.3
	≥ 39°C	2	16.7	5	41.7
Treatment	none	11	91.7	9	75.0
	Rehydration	1	8.3	3	25.0
	Hospitalization	0	0.0	0	0.0
Dehydration	none	12	100	10	83.3
	1-5%	0	0.0	2	16.7
	≥ 6%	0	0.0	0	0.0

Notes: N = number of subjects included in each group
N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD= standard deviation

Supplement 10: Percentage of subjects reporting RV GE (any intensity) and efficacy of the vaccine during the first efficacy follow-up period, by type (ATP efficacy cohort)

Type	Group	N	n	T (year)	n / T value	n / T 95%CI		n / N rate	n / N 95%CI		Vaccine efficacy %	Vaccine efficacy 95%CI	
ELISA													
G1	HRV	245	7*	112.4	0.062	0.030	0.131	2.9	1.2	5.8	64.9	-2.3	88.6
	Placebo	123	10 *	55.6	0.180	0.097	0.334	8.1	4.0	14.4			
RT-PCR													
G1	HRV	245	12	110.5	0.109	0.062	0.191	4.9	2.6	8.4	39.8	-55.7	76.1
	Placebo	123	10	55.6	0.180	0.097	0.334	8.1	4.0	14.4			
ELISA or RT-PCR													
G2	HRV	245	0	113.4	0.000	NE		0.0	0.0	1.5	100	-1858	100
	Placebo	123	1	56.7	0.018	0.002	0.130	0.8	0.0	4.4			
ELISA or RT-PCR													
G9	HRV	245	0	113.4	0.000	NE		0.0	0.0	1.5	100	-1858	100
	Placebo	123	1	56.7	0.018	0.002	0.130	0.8	0.0	4.4			

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode, in each group
n/N = percentage of subjects reporting at least one RV GE episode in each group
n/T = person-year rate of RV GE symptom in each group
NE = can not be estimated 95%CI= 95%confidence intervals
*Type is not known for one subject

Supplement 11: Percentage of subjects reporting severe RV GE and efficacy of the vaccine during the first efficacy follow-up period, by type (ATP efficacy cohort)

Type	Group	N	n	T (year)	n / T value	n / T 95%CI		n / N rate	n / N 95%CI		Vaccine efficacy %	Vaccine efficacy 95%CI	
ELISA or RT-PCR													
G1	HRV	245	1	113.2	0.009	0.001	0.063	0.4	0.0	2.3	87.4	-26.8	99.7
	Placebo	123	4	56.2	0.071	0.027	0.190	3.3	0.9	8.1			
ELISA or RT-PCR													
G2	HRV	245	0	113.4	0.000	NE		0.0	0.0	1.5	100	-1858	100
	Placebo	123	1	56.7	0.018	0.002	0.130	0.8	0.0	4.4			

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode, in each group
n/N = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE symptom in each group
NE = can not be estimated 95%CI = 95%confidence intervals

Supplement 12: Percentage of subjects hospitalized due to any GE and efficacy of the vaccine during the first efficacy follow-up period (ATP efficacy cohort)

			T	n / T			n / N			Vaccine efficacy			
Group	**N**	**n**	**(year)**	**value**	**95%CI**		**rate**	**95%CI**		**%**	**95%CI**		**p-value**
HRV	245	1	113.1	0.009	0.001	0.060	0.4	0.0	2.3	-infini	-infini	98.7	1.000
Placebo	123	0	56.9	0.000	NE		0.0	0.0	3.0				

Notes: N = number of subjects included in each group
n = number of subjects hospitalized due to GE in each group
T= sum of follow-up period expressed in year censored at the first occurrence of hospitalization due to GE, in each group
n/N= percentage of subjects hospitalized due to GE in each group
n/T= person-year rate of hospitalization due to GE in each group
95%CI= 95%confidence intervals
NE = can not be estimated p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 13: Number and percentage of subjects who reported GE episode(s) during the first efficacy follow-up period (total cohort)

Event	**Total number of episodes reported**	**HRV N = 255**		**Placebo N = 126**	
		n	**%**	**n**	**%**
GE	1	63	24.7	36	28.6
	2	19	7.5	6	4.8
	3	4	1.6	4	3.2
	Any	86	33.7	46	36.5
Rotavirus GE ELISA	1	8	3.1	13	10.3
	Any	8	3.1	13	10.3
RT-PCR	1	12	4.7	12	9.5
	Any	12	4.7	12	9.5

Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified symptom = sum of the "Total number of episode reported"

Supplement 14: Number of any GE episodes and RV GE episodes reported during the first efficacy follow-up period, by severity (total cohort)

Event	Severity	HRV n	HRV %	Placebo n	Placebo %
GE	Unknown	2	1.8	0	0.0
	Mild (1-6)	79	69.9	40	66.7
	Moderate (7-10)	27	23.9	12	20.0
	Severe (≥11)	5	4.4	8	13.3
	Any	113	100	60	100
Rotavirus GE					
ELISA	Mild (1-6)	2	25.0	3	23.1
	Moderate (7-10)	5	62.5	5	38.5
	Severe (≥11)	1	12.5	5	38.5
	Any	8	100	13	100
RT-PCR	Mild (1-6)	6	50.0	3	25.0
	Moderate (7-10)	5	41.7	4	33.3
	Severe (≥11)	1	8.3	5	41.7
	Any	12	100	12	100

Notes: n/% = number/percentage of the specified event reported in each group, by severity, among all specified events reported during the first efficacy follow-up period
Any = any specified symptom reported, regardless of severity

Supplement 15: Percentage of subjects with RV GE episodes reported during the first efficacy follow-up period, by type (total cohort)

Type	HRV N = 255 n	%	Placebo N = 126 n	%
ELISA				
Any	8	3.1	13	10.3
Unknown	1	0.4	1	0.8
G1	7	2.7	10	7.9
G2	0	0.0	1	0.8
G9	0	0.0	1	0.8
RT-PCR				
Any	12	4.7	12	9.5
G1	12	4.7	10	7.9
G2	0	0.0	1	0.8
G9	0	0.0	1	0.8

Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified type in each group
Any = number of subjects reporting at least one RV GE episode, whatever the type

Supplement 16: Characteristics of RV GE episodes reported during the first efficacy follow-up period, by ELISA (total cohort)

Characteristics	Parameters or categories	HRV N = 255 Value or n	%	Placebo N = 126 Value or n	%
	N'	8	-	13	-
Severity score	Mean	7.75	-	9.85	-
	SD	1.909	-	4.059	-
	Median	7.5	-	8.0	-
	Minimum	5	-	5	-
	Maximum	11	-	17	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	7	87.5	9	69.2
	5	1	12.5	2	15.4
	≥ 6 days	0	0.0	2	15.4
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	1-3	6	75.0	2	15.4
	4-5	0	0.0	4	30.8
	≥ 6	2	25.0	7	53.8
Duration of vomiting	0 day	1	12.5	2	15.4
	1 day	2	25.0	5	38.5
	2 days	4	50.0	2	15.4
	≥ 3 days	1	12.5	4	30.8
Maximum number of episodes of vomiting/24 hours	0	1	12.5	2	15.4
	1	2	25.0	3	23.1
	2-4	4	50.0	4	30.8
	≥ 5	1	12.5	4	30.8
Maximum fever reported/24 hours (measured rectally)	< 37.1°C	0	0.0	0	0.0
	37.1-38.4°C	4	50.0	4	30.8
	38.5-38.9°C	2	25.0	4	30.8
	≥ 39°C	2	25.0	5	38.5
Treatment	none	7	87.5	10	76.9
	Rehydration	1	12.5	3	23.1
	Hospitalization	0	0.0	0	0.0
Dehydration	none	8	100	11	84.6
	1-5%	0	0.0	2	15.4
	≥ 6%	0	0.0	0	0.0

Notes: N = number of subjects included in each group
N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter SD= standard deviation

Supplement 17: Characteristics of RV GE episodes reported during the first efficacy follow-up period, by RT-PCR (total cohort)

Characteristics	Parameters or categories	HRV N = 255 Value or n	%	Placebo N = 126 Value or n	%
	N'	12	-	12	-
Severity score	Mean	6.58	-	10.00	-
	SD	2.392	-	4.200	-
	Median	6.5	-	9.0	-
	Minimum	3	-	5	-
	Maximum	11	-	17	-
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	11	91.7	8	66.7
	5	1	8.3	2	16.7
	≥ 6 days	0	0.0	2	16.7
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	1-3	9	75.0	2	16.7
	4-5	1	8.3	3	25.0
	≥ 6	2	16.7	7	58.3
Duration of vomiting	0 day	4	33.3	2	16.7
	1 day	3	25.0	5	41.7
	2 days	4	33.3	1	8.3
	≥ 3 days	1	8.3	4	33.3
Maximum number of episodes of vomiting/24 hours	0	4	33.3	2	16.7
	1	2	16.7	3	25.0
	2-4	5	41.7	3	25.0
	≥ 5	1	8.3	4	33.3
Maximum fever reported/24 hours (measured rectally)	< 37.1°C	1	8.3	0	0.0
	37.1-38.4°C	5	41.7	3	25.0
	38.5-38.9°C	4	33.3	4	33.3
	≥ 39°C	2	16.7	5	41.7
Treatment	none	11	91.7	9	75.0
	Rehydration	1	8.3	3	25.0
	Hospitalization	0	0.0	0	0.0
Dehydration	none	12	100	10	83.3
	1-5%	0	0.0	2	16.7
	≥ 6%	0	0.0	0	0.0

Notes: N = number of subjects included in each group
N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter SD= standard deviation

Supplement 18: Duration (in years) of the follow-up periods for the first efficacy period (total cohort)

Duration (years) of follow-up period	**HRV**	**Placebo**
N	255	126
Total	118.0	58.2
Mean	0.463	0.462
Minimum	0.016	0.121
Q1	0.425	0.422
Median	0.468	0.468
Q3	0.518	0.521
Maximum	0.595	0.584

Notes: N = number of subjects included in each group
Total = sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 19: Percentage of subjects reporting RV GE (any intensity) and efficacy of the vaccine during the first efficacy follow-up period (total cohort)

Group	N	n	T (year)	n / T value	95%CI		n / N rate	95%CI		Vaccine efficacy %	95%CI		p-value
ELISA													
HRV	255	8	116.8	0.068	0.034	0.137	3.1	1.4	6.1	69.6	20.9	89.1	0.007
Placebo	126	13	56.5	0.230	0.134	0.397	10.3	5.6	17.0				
RT-PCR													
HRV	255	12	115.2	0.104	0.059	0.183	4.7	2.5	8.1	50.6	-20.2	79.7	0.076
Placebo	126	12	56.6	0.212	0.120	0.373	9.5	5.0	16.0				

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode, in each group
n/N = percentage of subjects reporting at least one RV GE episode in each group
n/T= person-year rate of RV GE in each group
95%CI = 95%confidence intervals p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 20: Percentage of subjects reporting severe RV GE and efficacy of the vaccine during the first efficacy follow-up period (total cohort)

Group	N	n	T (year)	n / T value	95%CI		n / N rate	95%CI		Vaccine efficacy %	95%CI		p-value
ELISA or RT-PCR													
HRV	255	1	118.0	0.008	0.001	0.060	0.4	0.0	2.2	90.1	11.7	99.8	0.016
Placebo	126	5	57.4	0.087	0.036	0.209	4.0	1.3	9.0				

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode, in each group
n/N = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE in each group
95%CI = 95%confidence intervals p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 21: Percentage of subjects reporting RV GE (any intensity) and efficacy of the vaccine during the first efficacy follow-up period, by type (total cohort)

Type	Group	N	n	T (year)	n / T value	n / T 95%CI		n / N rate	n / N 95%CI		Vaccine efficacy %	Vaccine efficacy 95%CI	
ELISA													
G1	HRV	255	7*	117.1	0.060	0.028	0.125	2.7	1.1	5.6	65.4	-0.7	88.8
	Placebo	126	10*	56.9	0.176	0.095	0.326	7.9	3.9	14.1			
RT-PCR													
G1	HRV	255	12	115.2	0.104	0.059	0.183	4.7	2.5	8.1	40.7	-53.2	76.5
	Placebo	126	10	56.9	0.176	0.095	0.326	7.9	3.9	14.1			
ELISA or RT-PCR													
G2	HRV	255	0	118.1	0.000	NE		0.0	0.0	1.4	100	-1827	100
	Placebo	126	1	58.0	0.017	0.002	0.120	0.8	0.0	4.3			
ELISA or RT-PCR													
G9	HRV	255	0	118.1	0.000	NE		0.0	0.0	1.4	100	-1827	100
	Placebo	126	1	58.0	0.017	0.002	0.120	0.8	0.0	4.3			

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode, in each group
n/N = percentage of subjects reporting at least one RV GE episode in each group
n/T = person-year rate of RV GE symptom in each group
NE = can not be estimated 95%CI = 95%confidence intervals
*Type is not known for one subject

Supplement 22: Percentage of subjects reporting severe RV GE and efficacy of the vaccine during the first efficacy follow-up period, by type (total cohort)

Type	Group	N	n	T (year)	n / T value	n / T 95%CI		n / N rate	n / N 95%CI		Vaccine efficacy %	Vaccine efficacy 95%CI	
ELISA or RT-PCR													
G1	HRV	255	1	118.0	0.008	0.001	0.060	0.4	0.0	2.2	87.6	-24.8	99.7
	Placebo	126	4	57.5	0.070	0.026	0.185	3.2	0.9	7.9			
ELISA or RT-PCR													
G2	HRV	255	0	118.1	0.000	NE		0.0	0.0	1.4	100	-1827	100
	Placebo	126	1	58.0	0.017	0.002	0.120	0.8	0.0	4.3			

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode, in each group
n/N = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE symptom in each group
NE = can not be estimated 95%CI = 95%confidence intervals

Supplement 23: Percentage of subjects hospitalized due to any GE and efficacy of the vaccine during the first efficacy follow-up period (total cohort)

			T	n / T			n / N			Vaccine efficacy			
Group	**N**	**n**	**(year)**	**value**	**95%CI**		**rate**	**95%CI**		**%**	**95%CI**		**p-value**
HRV	255	1	117.8	0.008	0.001	0.060	0.4	0.0	2.2	-infini	-infini	98.7	1.000
Placebo	126	0	58.2	0.000	NE		0.0	0.0	2.9				

Notes: N = number of subjects included in each group
n = number of subjects hospitalized due to GE in each group
T = sum of follow-up period expressed in year censored at the first occurrence of hospitalization due to GE, in each group
n/N = percentage of subjects hospitalized due to GE in each group
n/T = person-year rate of hospitalization due to GE in each group
95%CI = 95%confidence intervals NE = can not be estimated
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 24: Percentage of subjects reporting asymptomatic RV infection and efficacy of the vaccine during the first efficacy follow-up period (total cohort)

Group	N	n	%	95%CI		Vaccine efficacy %	95%CI		p-value
ELISA									
HRV	203	2	1.0	0.1	3.5	88.5	44.5	98.8	0.001
Placebo	105	9	8.6	4.0	15.6				
RT-PCR									
HRV	201	2	1.0	0.1	3.5	89.5	50.5	98.9	0.001
Placebo	106	10	9.4	4.6	16.7				

Notes: N = number of subjects included in each group with available anti-rotavirus IgA antibody concentrations at Visits 3 and 4 and who did not reported a RV GE episode between Visit 3 and Visit 4
n = number of subjects reporting asymptomatic RV infection in each group
% = percentage of subjects reporting asymptomatic RV infection in each group
95%CI = 95%confidence intervals p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 25: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) rated as grade 3 in intensity during the 15-day solicited follow-up period (total cohort)

		Symptoms				
		N	**n**	**%**	**95% CI**	
					L.L.	**U.L.**
Dose 1	HRV	267	24	9.0	5.8	13.1
	Placebo	133	6	4.5	1.7	9.6
Dose 2	HRV	255	18	7.1	4.2	10.9
	Placebo	124	12	9.7	5.1	16.3
Overall doses	HRV	522	42	8.0	5.9	10.7
	Placebo	257	18	7.0	4.2	10.8
Overall subjects	HRV	267	40	15.0	10.9	19.8
	Placebo	133	18	13.5	8.2	20.5

Notes: 95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit
Each dose:
N = number of documented doses, for the considered dose
(a documented dose is defined as a dose for which a symptom sheet was completed and/or an unsolicited symptom was reported)
n/% = number/percentage of documented doses leading to reporting of at least one grade 3 symptom, for the considered dose
Overall/dose:
N = total number of documented doses
n/% = total number/percentage of documented doses leading to reporting of at least one grade 3 symptom
Overall/subject
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting at least one grade 3 symptom

Supplement 26: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15-day solicited follow-up period (total cohort)

		Symptoms				
		N	**n**	**%**	**95% CI**	
					L.L.	**U.L.**
Dose 1	HRV	267	150	56.2	50.0	62.2
	Placebo	133	62	46.6	37.9	55.5
Dose 2	HRV	255	139	54.5	48.2	60.7
	Placebo	124	65	52.4	43.3	61.5
Overall doses	HRV	522	289	55.4	51.0	59.7
	Placebo	257	127	49.4	43.1	55.7
Overall subjects	HRV	267	193	72.3	66.5	77.6
	Placebo	133	86	64.7	55.9	72.7

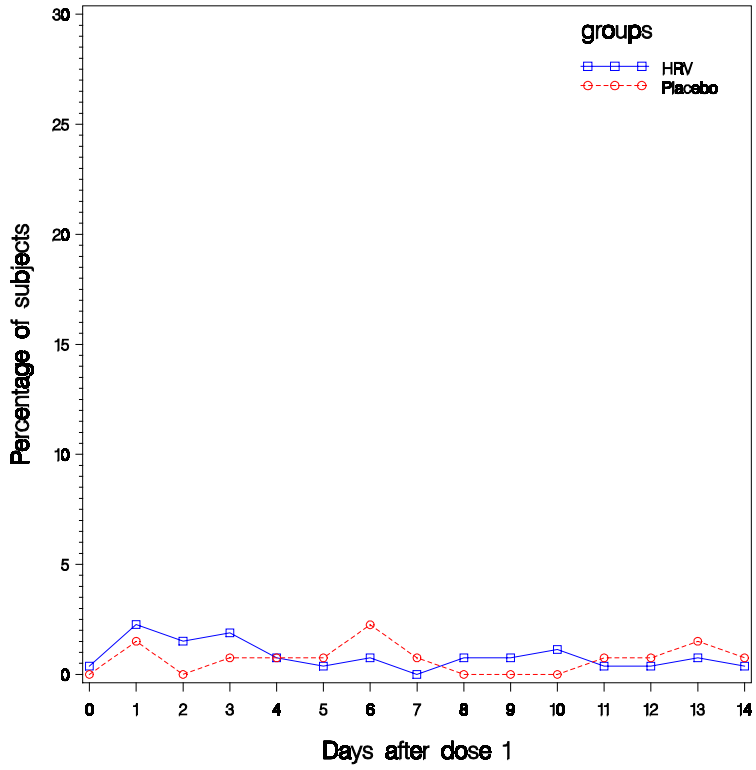
Notes: 95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit
Each dose:
N = number of documented doses, for the considered dose
(a documented dose is defined as a dose for which a symptom sheet was completed and/or an unsolicited symptom was reported)
n/% = number/percentage of documented doses leading to reporting of at least one symptom assessed as related to vaccination, for the considered dose
Overall/dose:
N = total number of documented doses
n/% = total number/percentage of documented doses leading to reporting of at least one symptom assessed as related to vaccination
Overall/subject
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting at least one symptom assessed as related to vaccination

Supplement 27: Percentage of doses reporting each solicited symptom including those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after each dose (total cohort)

Dose		**1**								**2**							
		HRV (N = 265)				**Placebo (N= 133)**				**HRV (N = 255)**				**Placebo (N= 124)**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
				L.L.	**UL**			**L.L.**	**U.L.**			**L.L.**	**U.L.**			**L.L.**	**U.L.**
Diarrhea	Total	20	7.5	4.7	11.4	7	5.3	2.1	10.5	11	4.3	2.2	7.6	2	1.6	0.2	5.7
	Grade 3	4	1.5	0.4	3.8	0	0.0	0.0	2.7	1	0.4	0.0	2.2	0	0.0	0.0	2.9
	Related	16	6.0	3.5	9.6	5	3.8	1.2	8.6	10	3.9	1.9	7.1	1	0.8	0.0	4.4
Irritability	Total	163	61.5	55.4	67.4	80	60.2	51.3	68.5	150	58.8	52.5	64.9	66	53.2	44.1	62.2
	Grade 3	14	5.3	2.9	8.7	5	3.8	1.2	8.6	9	3.5	1.6	6.6	7	5.6	2.3	11.3
	Related	129	48.7	42.5	54.9	55	41.4	32.9	50.2	114	44.7	38.5	51.0	48	38.7	30.1	47.9
Loss of appetite	Total	64	24.2	19.1	29.8	22	16.5	10.7	24.0	60	23.5	18.5	29.2	25	20.2	13.5	28.3
	Grade 3	0	0.0	0.0	1.4	0	0.0	0.0	2.7	1	0.4	0.0	2.2	0	0.0	0.0	2.9
	Related	47	17.7	13.3	22.9	14	10.5	5.9	17.0	42	16.5	12.1	21.6	17	13.7	8.2	21.0
Fever	Total	32	12.1	8.4	16.6	14	10.5	5.9	17.0	69	27.1	21.7	33.0	31	25.0	17.7	33.6
	Grade 3	0	0.0	0.0	1.4	0	0.0	0.0	2.7	1	0.4	0.0	2.2	0	0.0	0.0	2.9
	Related	22	8.3	5.3	12.3	7	5.3	2.1	10.5	39	15.3	11.1	20.3	14	11.3	6.3	18.2
Vomiting	Total	23	8.7	5.6	12.7	6	4.5	1.7	9.6	16	6.3	3.6	10.0	11	8.9	4.5	15.3
	Grade 3	6	2.3	0.8	4.9	0	0.0	0.0	2.7	6	2.4	0.9	5.1	2	1.6	0.2	5.7
	Related	18	6.8	4.1	10.5	5	3.8	1.2	8.6	12	4.7	2.5	8.1	8	6.5	2.8	12.3

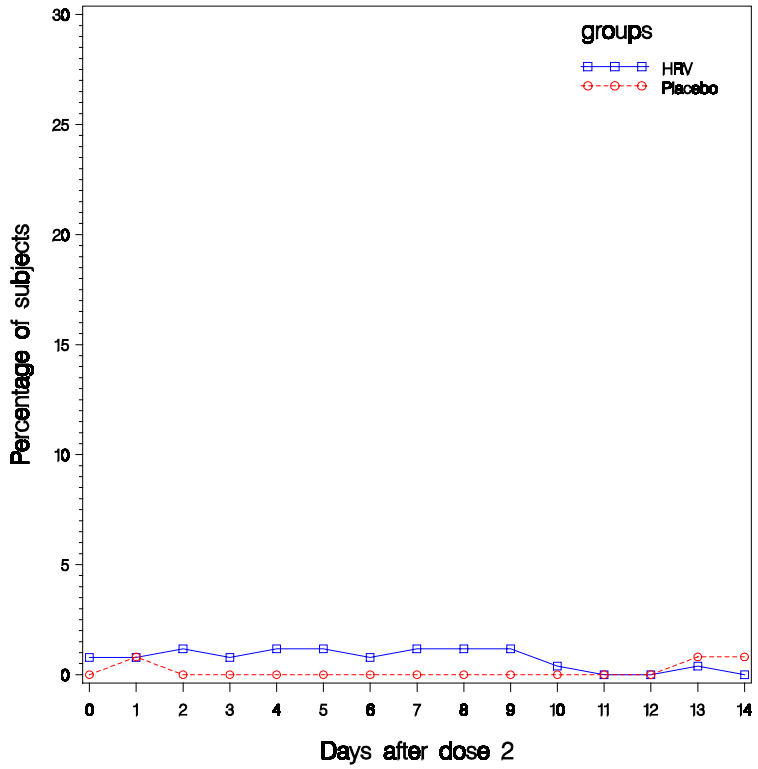
Notes: N = number of solicited symptom sheets completed for a considered dose
n/% = number/percentage of doses leading to reporting of the specified symptom, for a considered dose
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit

Supplement 28: Prevalence of diarrhea by day after Dose 1, during the solicited follow-up period (total cohort)



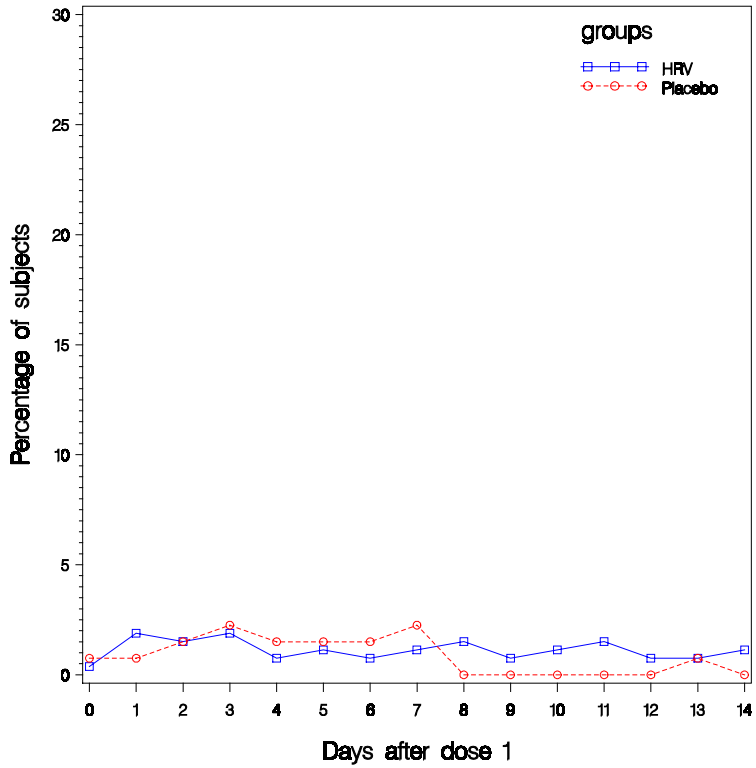
Notes: Day 0= day of vaccination, Day 1= one day after vaccination,…
Y-axis was cut at 30%

Supplement 29: Prevalence of diarrhea by day after Dose 2, during the solicited follow-up period (total cohort)



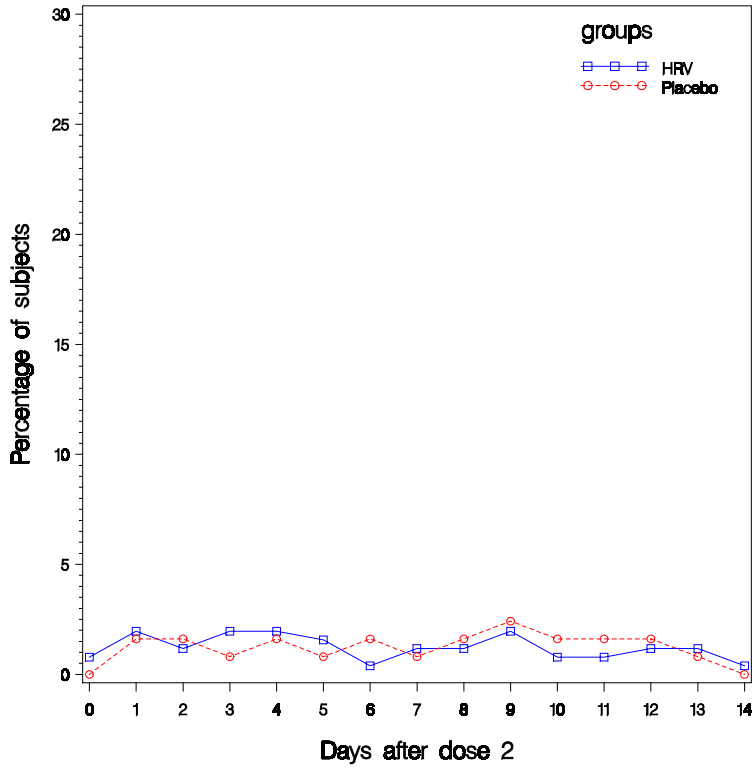
Notes: Day 0= day of vaccination, Day 1= one day after vaccination,…
Y-axis was cut at 30%

Supplement 30: Prevalence of vomiting by day after Dose 1, during the solicited follow-up period (total cohort)



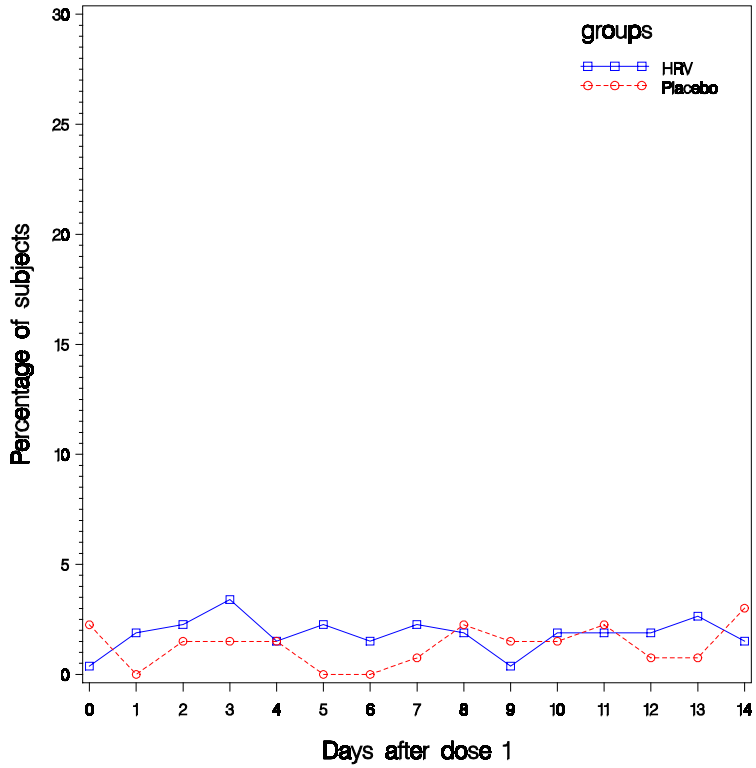
Notes: Day 0= day of vaccination, Day 1= one day after vaccination,…
Y-axis was cut at 30%

Supplement 31: Prevalence of vomiting by day after Dose 2, during the solicited follow-up period (total cohort)



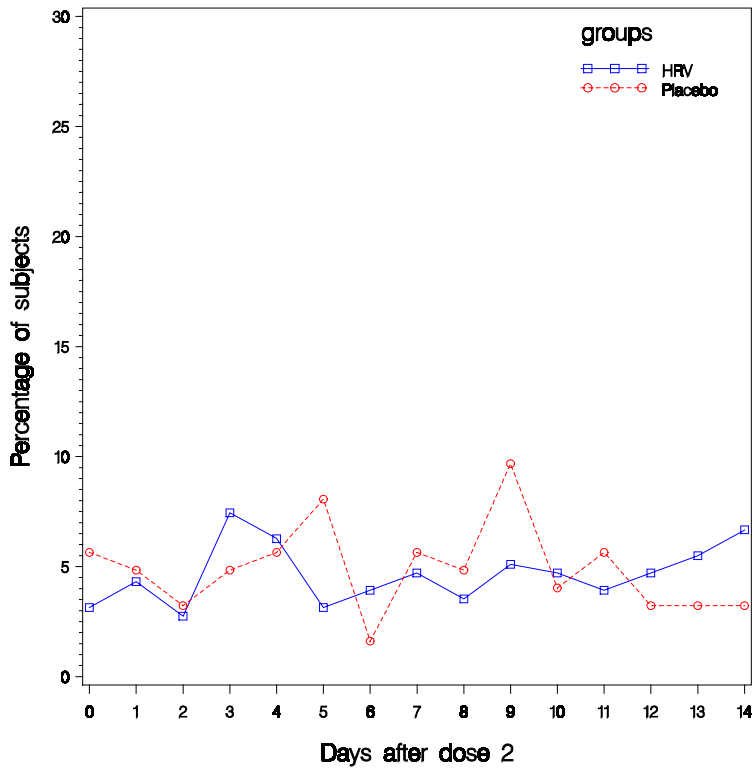
Notes: Day 0= day of vaccination, Day 1= one day after vaccination,…
Y-axis was cut at 30%

Supplement 32: Prevalence of fever by day after Dose 1, during the solicited follow-up period (total cohort)



Notes: Day 0= day of vaccination, Day 1= one day after vaccination,…
Y-axis was cut at 30%

Supplement 33: Prevalence of fever by day after Dose 2, during the solicited follow-up period (total cohort)



Notes: Day 0= day of vaccination, Day 1= one day after vaccination,…
Y-axis was cut at 30%

Supplement 34: Duration (in days) of diarrhea during the solicited follow-up period (total cohort)

Duration (days) of diarrhea	**Dose 1**		**Dose 2**	
	HRV	**Placebo**	**HRV**	**Placebo**
n	20	7	11	2
Mean	1.65	2.00	2.55	1.50
Minimum	1	1	1	1
Q1	1	1	1	1
Median	1	2	1	1.5
Q3	2	3	3	2
Maximum	6	4	10	2

Notes: n = number of subjects reporting diarrhea
Q1= 25th percentile Q3=75th percentile

Supplement 35: Duration (in days) of vomiting during the solicited follow-up period (total cohort)

Duration (days) of vomiting	**Dose 1**		**Dose 2**	
	HRV	**Placebo**	**HRV**	**Placebo**
n	23	6	16	11
Mean	1.96	2.83	2.94	2.09
Minimum	1	1	1	1
Q1	1	1	1	1
Median	1	2.5	1	2
Q3	2	4	5	3
Maximum	11	6	9	4

Notes: n = number of subjects reporting vomiting
Q1= 25th percentile Q3=75th percentile

Supplement 36: Duration (in days) of fever during the solicited follow-up period (total cohort)

Duration (days) of fever	**Dose 1**		**Dose 2**	
	HRV	**Placebo**	**HRV**	**Placebo**
n	32	14	69	31
Mean	2.28	1.86	2.58	2.94
Minimum	1	1	1	1
Q1	1	1	1	1
Median	1	1	2	2
Q3	3	2	3	4
Maximum	8	7	12	13

Notes: n = number of subjects reporting fever
Q1= 25th percentile Q3=75th percentile

Supplement 37: Summary of solicited gastrointestinal symptoms (diarrhea and vomiting) and fever for subjects who reported both diarrhea and vomiting during the 15-day solicited follow-up period (total cohort)

Previous dose	**Solicited gastrointestinal symptoms (diarrhea and vomiting) and fever**	**Presence of RV in stool samples by ELISA (by RT-PCR)**
1	Diarrhea on Day 1 (grade 1) Vomiting on Day 1 (grade 1) No fever	No stool sample collected
1	Diarrhea on Day 1 (grade 1) Vomiting on Day 2 (grade 2), 3 (grade 1), 7 (grade 2) and 12 (grade 2) No fever	Negative (not tested)
1	Diarrhea on Days 0 to 3 (grade 3) Vomiting on Days 1 and 2 (grade 3) No fever	Negative (Positive, G1)
1	Diarrhea on Day 10 (grade 1) Vomiting on Days 4 to 14 (grade 3) No fever	Invalid result (not tested)
1	Diarrhea on Day 2 (grade 1) Vomiting on Days 1, 3 and 5 (grade 1) No fever	Positive (positive, G1)
1	Diarrhea on Days 3 and 4 (grade 1) Vomiting on Days 3 and 4 (grade 1) No fever	No stool sample collected
2	Diarrhea on Day 4 (grade 1) Vomiting on Day 5 (grade 3) No fever	Negative (Negative)

Supplement 38: Number of GE episodes reported from day of Dose 1 till Day 14 after Dose 2 (total cohort)

Group	**Between dose 1 and dose 2** **n**	**Between dose 2 and day 14 after dose 2** **n**	**On combined doses** **n**
HRV (N=267)	57	28	85
Placebo (N=133)	23	13	36

N = number of subjects with at least one documented dose
n= number of GE episodes reported during the specified period

Supplement 39: Number of subjects reporting GE episode from day of Dose 1 till Day 14 after Dose 2 (total cohort)

Group	Between dose 1 and dose 2					Between dose 2 and day 14 after dose 2					On combined doses				
				95%CI					95%CI					95%CI	
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
HRV	267	46	17.2	12.9	22.3	255	26	10.2	6.8	14.6	267	64	24.0	19.0	29.6
Placebo	133	16	12.0	7.0	18.8	124	13	10.5	5.7	17.3	133	23	17.3	11.3	24.8

N = number of subjects with at least one documented dose during the specified period
n/% = number/percentage of subjects reporting at least one GE episode during the specified period
95% CI, L.L and U.L = lower and upper limits of the exact 95% CI

Supplement 40: Number of GE episodes reported from day of Dose 1 till Day 14 after Dose 2, by stool results (total cohort)

	HRV		Placebo	
Stool results	**n**	**%**	**n**	**%**
ELISA				
No stools collected	30	35.3	11	30.6
Stools collected but no results available	2	2.4	0	0.0
Negative	44	51.8	25	69.4
Positive	9	10.6	0	0.0
Total	85	100	36	100
RT-PCR				
No stools collected	30	35.3	11	30.6
Stools collected but no results available	27	31.8	16	44.4
Negative	9	10.6	9	25.0
Positive	19	22.4	0	0.0
Total	85	100	36	100

Total = number of GE episodes reported
n/% = number/percentage of GE episodes reported, by category

Supplement 41: Number of subjects reporting RV GE episode from day of Dose 1 till Day 14 after Dose 2 (total cohort)

Group	Between dose 1 and dose 2					Between dose 2 and day 14 after dose 2					On combined doses				
				95%CI					95%CI					95%CI	
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
ELISA															
HRV	267	9	3.4	1.6	6.3	255	0	0.0	0.0	1.4	267	9	3.4	1.6	6.3
Placebo	133	0	0.0	0.0	2.7	124	0	0.0	0.0	2.9	133	0	0.0	0.0	2.7
RT-PCR															
HRV	267	12	4.5	2.3	7.7	255	6	2.4	0.9	5.1	267	17	6.4	3.8	10.0
Placebo	133	0	0.0	0.0	2.7	124	0	0.0	0.0	2.9	133	0	0.0	0.0	2.7

N = number of subjects with at least one documented dose during the specified period
n/% = number/percentage of subjects reporting at least one RV GE episode during the specified period
95% CI, L.L and U.L = lower and upper limits of the exact 95% CI

Supplement 42: Summary of RV GE episodes as detected by ELISA during the period starting from the day of Dose 1 and ending 2 weeks after Dose 2 (total cohort)

Previous dose	**Day of onset of the GE**	**End Day of the GE**
1	Day 4	Day 4
1	Day 1	Day 1
1	Day 3	Day 3
1	Day 2	Day 2
1	Day 3	Day 3
1	Day 9	Day 11
1	Day 8	Day 8
1	Day 22	Day 26
1	Day 1	Day 5

Supplement 43: Summary of RV GE episodes as detected by RT-PCR during the period starting from the day of Dose 1 and ending 2 weeks after Dose 2 (total cohort)

Previous dose	Day of onset of the GE	End Day of the GE	G type by RT-PCR
1	Day 4	Day 4	G1
1	Day 0	Day 0	G1
1	Day 1	Day 1	G1
1	Day 3	Day 3	G1
1	Day 0	Day 3	G1
1	Day 2	Day 2	G1
1	Day 3	Day 3	G1
1	Day 40	Day 41	G1
1	Day 9	Day 11	G1
1	Day 8	Day 8	G1
1	Day 22	Day 26	G1
1	Day 1	Day 2	G1
1	Day 1	Day 5	G1
2	Day 0	Day 0	G1
2	Day 13	Day 13	G1
2	Day 0	Day 4	G1
2	Day 2	Day 2	G1
2	Day 0	Day 9	G1
2	Day 7	Day 12	G1

Supplement 44: Number of RV GE episodes in the HRV vaccine group, from day of Dose 1 till Day 14 after Dose 2, by severity (total cohort)

Severity	HRV n	HRV %
ELISA		
Unknown	2*	22.2
Mild (1-6)	7	77.8
Moderate (7-10)	0	0.0
Severe (≥11)	0	0.0
Any	9	100
RT-PCR		
Unknown	4*§	21.1
Mild (1-6)	13	68.4
Moderate (7-10)	2	10.5
Severe (≥11)	0	0.0
Any	19	100

* one subject reported a GE episode as unsolicited symptoms starting on day 22 after dose 1. The intensity of this symptom was set as grade 2, with a duration of 4 days. Another subject reported a GE episode during the solicited follow-up period after dose 1 with a global score being 6 or 7.
§ one subject reported diarrhea and vomiting as unsolicited symptoms starting on day 40 after dose 1. The intensity of these symptoms were set as grade 1, with a duration of 1 day. Another subject reported a GE episode during the solicited follow-up period after dose 1 with a global score being 6 or 7.

Supplement 45: The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV N = 267				Placebo N = 133				p-value
				95% CI				95% CI		
		n	%	L.L.	U.L.	n	%	L.L.	U.L.	
At least one symptom		190	71.2	65.3	76.5	93	69.9	61.4	77.6	0.816
Application site (1820)	Dermatitis contact (0049)	2	0.7	0.1	2.7	0	0	0	2.7	1.000
	Injection site pain (0057)	0	0	0	1.4	1*	0.8	0	4.1	0.333
Body as a whole general (1810)	Allergic reaction (0712)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Allergy (1058)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Crying abnormal (1162)	7	2.6	1.1	5.3	6	4.5	1.7	9.6	0.372
	Fatigue (0724)	11	4.1	2.1	7.3	5	3.8	1.2	8.6	1.000
	Fever (0725)	37	13.9	9.9	18.6	14	10.5	5.9	17.0	0.427
	Injury (9001)	1	0.4	0	2.1	2	1.5	0.2	5.3	0.258
	Pain (0730)	11	4.1	2.1	7.3	3	2.3	0.5	6.5	0.403
Cardiovascular general (1010)	Heart disorder (0504)	0	0	0	1.4	2	1.5	0.2	5.3	0.110
Central and peripheral nervous system (410)	Dysphonia (0103)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Headache (0109)	1	0.4	0	2.1	0	0	0	2.7	1.000
Fetal (1500)	Hernia congenital (0885)	1	0.4	0	2.1	0	0	0	2.7	1.000

Notes: N = number of subjects with at least one documented dose n/%= number/percentage of subjects reporting at least once the specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO Preferred terms
95% CI: exact 95% confidence interval
p-value = two-sided Fisher's exact test (significant level of α=0.05)
*Following DTP vaccination

Supplement 45 (continued): The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV N = 267				Placebo N = 133				p-value
				95% CI				95% CI		
		n	%	L.L.	U.L.	n	%	L.L.	U.L.	
Gastrointestinal system (600)	Abdominal pain (0268)	11	4.1	2.1	7.3	3	2.3	0.5	6.5	0.403
	Anorexia (0165)	3	1.1	0.2	3.2	0	0	0	2.7	0.554
	Appetite increased (0168)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Constipation (0204)	9	3.4	1.6	6.3	2	1.5	0.2	5.3	0.350
	Diarrhea (0205)	7	2.6	1.1	5.3	2	1.5	0.2	5.3	0.724
	Dyspepsia (0279)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Flatulence (0285)	17	6.4	3.8	10	4	3.0	0.8	7.5	0.233
	GE (0293)	2	0.7	0.1	2.7	0	0	0	2.7	1.000
	Gastroesophageal reflux (1149)	18	6.7	4.0	10.4	4	3.0	0.8	7.5	0.163
	Melena (0306)	1	0.4	0	2.1	2	1.5	0.2	5.3	0.258
	Stomatitis (0327)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Tongue disorder (0330)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Tooth ache (1376)	6	2.2	0.8	4.8	5	3.8	1.2	8.6	0.517
	Vomiting (0228)	4	1.5	0.4	3.8	2	1.5	0.2	5.3	1.000

Notes: N = number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the specified unsolicited symptom
95% CI: exact 95% confidence interval
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 45 (continued): The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	**WHO Preferred term (CODE)**	**HRV N = 267**				**Placebo N = 133**				**p-value**
				95% CI				**95% CI**		
		s	**%**	**L.L.**	**U.L.**	**s**	**%**	**L.L.**	**U.L.**	
Hearing and vestibular (432)	Ear disorder nos (1255)	1	0.4	0	2.1	0	0	0	2.7	1.000
Metabolic and nutritional (800)	Growth retarded (0379)	1	0.4	0	2.1	2	1.5	0.2	5.3	0.258
	Thirst (0405)	1	0.4	0	2.1	0	0	0	2.7	1.000
Neonatal and infancy (1600)	Feeding disorder neonatal (0909)	1	0.4	0	2.1	0	0	0	2.7	1.000
Platelet bleeding and clotting (1230)	Purpura (0459)	1	0.4	0	2.1	0	0	0	2.7	1.000
Psychiatric (500)	Insomnia (0183)	5	1.9	0.6	4.3	2	1.5	0.2	5.3	1.000
	Nervousness (0188)	64	24.0	19.0	29.6	31	23.3	16.4	31.4	1.000
	Sleep disorder (0195)	1	0.4	0	2.1	1	0.8	0	4.1	1.000
	Somnolence (0197)	2	0.7	0.1	2.7	2	1.5	0.2	5.3	0.630

Notes: N = number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the specified unsolicited symptom
95% CI: exact 95% confidence interval
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 45 (continued): The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV N = 267				Placebo N = 133				p-value
				95% CI				95% CI		
		n	%	L.L.	U.L.	n	%	L.L.	U.L.	
Resistance mechanism (1830)	Abscess (0887)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Infection (0736)	2	0.7	0.1	2.7	0	0	0	2.7	1.000
	Infection bacterial (0738)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Infection fungal (0739)	2	0.7	0.1	2.7	0	0	0	2.7	1.000
	Infection viral (0740)	7	2.6	1.1	5.3	4	3.0	0.8	7.5	1.000
	Moniliasis (0741)	6	2.2	0.8	4.8	0	0	0	2.7	0.185
	Otitis media (0750)	22	8.2	5.2	12.2	8	6.0	2.6	11.5	0.547
	Upper resp tract infection (0543)	25	9.4	6.2	13.5	11	8.3	4.2	14.3	0.853
Respiratory system (1100)	Asthma (1367)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Bronchitis (0805)	2	0.7	0.1	2.7	1	0.8	0	4.1	1.000
	Coughing (0513)	26	9.7	6.5	13.9	9	6.8	3.1	12.5	0.355

Notes: N = number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the specified unsolicited symptom
95% CI: exact 95% confidence interval
p-value = two-sided Fisher's exact test (significant level of α=0.05)

upplement 45 (continued): The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV N = 267				Placebo N = 133				p-value
				95% CI				95% CI		
		n	%	L.L.	U.L.	n	%	L.L.	U.L.	
Respiratory system (1100)	Dyspnea (0514)	2	0.7	0.1	2.7	0	0	0	2.7	1.000
	Laryngitis (0521)	1	0.4	0	2.1	1	0.8	0	4.1	1.000
	Pharyngitis (0523)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Pneumonia (0528)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Rhinitis (0539)	70	26.2	21.0	31.9	29	21.8	15.1	29.8	0.390
Skin and appendages (100)	Bullous eruption (0871)	0	0	0	1.4	1	0.8	0	4.1	0.333
	Eczema (0012)	9	3.4	1.6	6.3	4	3.0	0.8	7.5	1.000
	Nail disorder (0020)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Pigmentation abnormal (0973)	0	0	0	1.4	1	0.8	0	4.1	0.333

Notes: N = number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the specified unsolicited symptom
95% CI: exact 95% confidence interval
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 45 (continued): The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV N = 267				Placebo N = 133				p-value
				95% CI				95% CI		
		n	%	L.L.	U.L.	n	%	L.L.	U.L.	
Skin and appendages (100)	Pruritus (0024)	1	0.4	0	2.1	0	0	0	2.7	1.000
	Rash (0027)	6	2.2	0.8	4.8	2	1.5	0.2	5.3	1.000
	Rash erythematous (0028)	1	0.4	0	2.1	1	0.8	0	4.1	1.000
	Seborrhea (0033)	0	0	0	1.4	1	0.8	0	4.1	0.333
	Skin disorder (0037)	1	0.4	0	2.1	2	1.5	0.2	5.3	0.258
	Skin dry (1123)	0	0	0	1.4	1	0.8	0	4.1	0.333
Vision (431)	Conjunctivitis (0238)	20	7.5	4.6	11.3	17	12.8	7.6	19.7	0.100

Notes: N = number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the specified unsolicited symptom
95% CI: exact 95% confidence interval
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 46: The percentage of doses with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	**WHO Preferred term (CODE)**	**HRV D = 522**				**Placebo D = 257**			
				95% CI				**95% CI**	
		d	**%**	**L.L.**	**U.L.**	**d**	**%**	**L.L.**	**U.L.**
At least one symptom		42	8	5.9	10.7	16	6.2	3.6	9.9
Body as a whole general (1810)	Crying abnormal (1162)	1	0.2	0	1.1	2	0.8	0.1	2.8
	Fatigue (0724)	5	1.0	0.3	2.2	5	1.9	0.6	4.5
	Pain (0730)	1	0.2	0	1.1	0	0	0	1.4
Gastrointestinal system (600)	Abdominal pain (0268)	9	1.7	0.8	3.2	1	0.4	0	2.1
	Constipation (0204)	1	0.2	0	1.1	0	0	0	1.4
	Flatulence (0285)	10	1.9	0.9	3.5	1	0.4	0	2.1
	Gastroesophageal reflux (1149)	15	2.9	1.6	4.7	3	1.2	0.2	3.4
Metabolic and nutritional (800)	Growth retarded (0379)	0	0	0	0.7	1	0.4	0	2.1
Neonatal and infancy (1600)	Feeding disorder neonatal (0909)	1	0.2	0	1.1	0	0	0	1.4
Platelet bleeding and clotting (1230)	Purpura (0459)	1	0.2	0	1.1	0	0	0	1.4
Psychiatric (500)	Insomnia (0183)	2	0.4	0	1.4	2	0.8	0.1	2.8
	Sleep disorder (0195)	1	0.2	0	1.1	1	0.4	0	2.1
	Somnolence (0197)	2	0.4	0	1.4	1	0.4	0	2.1
Skin and appendages (100)	Bullous eruption (0871)	0	0	0	0.7	1	0.4	0	2.1

Notes: D = total number of documented doses
d/% = number/percentage of doses leading to reporting of at least one report of the specified unsolicited symptom
At least one symptom = total number of doses followed by at least one report of an unsolicited symptom, assessed as related to vaccination, whatever the WHO Preferred terms
95% CI: exact 95% confidence interval

Supplement 47: The percentage of doses with grade 3 unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	**WHO Preferred term (CODE)**	**HRV D = 522**				**Placebo D = 257**			
				95% CI				**95% CI**	
		d	**%**	**L.L.**	**U.L.**	**d**	**%**	**L.L.**	**U.L.**
At least one symptom		18	3.4	2.1	5.4	13	5.1	2.7	8.5
Body as a whole general (1810)	Crying abnormal (1162)	1	0.2	0	1.1	3	1.2	0.2	3.4
	Fatigue (0724)	0	0	0	0.7	1	0.4	0	2.1
	Fever (0725)	3	0.6	0.1	1.7	1	0.4	0	2.1
	Injury (9001)	0	0	0	0.7	1	0.4	0	2.1
Gastrointestinal system (600)	Abdominal pain (0268)	1	0.2	0	1.1	1	0.4	0	2.1
	Flatulence (0285)	4	0.8	0.2	2	0	0	0	1.4
	Gastroesophageal reflux (1149)	1	0.2	0	1.1	0	0	0	1.4
	Melena (0306)	0	0	0	0.7	1	0.4	0	2.1
Psychiatric (500)	Insomnia (0183)	1	0.2	0	1.1	0	0	0	1.4
	Nervousness (0188)	2	0.4	0	1.4	0	0	0	1.4
Resistance mechanism (1830)	Infection viral (0740)	1	0.2	0	1.1	0	0	0	1.4
	Otitis media (0750)	1	0.2	0	1.1	2	0.8	0.1	2.8
	Upper resp tract infection (0543)	3	0.6	0.1	1.7	2	0.8	0.1	2.8

Notes: D = total number of documented doses
d/% = number/percentage of doses leading to reporting of at least one report of the specified unsolicited symptom
At least one symptom = total number of doses followed by at least one report of a grade 3 unsolicited symptom, whatever the WHO Preferred terms
95% CI: exact 95% confidence interval

Supplement 47 (continued): The percentage of doses with grade 3 unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	**WHO Preferred term (CODE)**	**HRV D = 522**				**Placebo D = 257**			
				95% CI				**95% CI**	
		d	**%**	**L.L.**	**U.L.**	**d**	**%**	**L.L.**	**U.L.**
Respiratory system (1100)	Coughing (0513)	2	0.4	0	1.4	2	0.8	0.1	2.8
	Laryngitis (0521)	0	0	0	0.7	1	0.4	0	2.1
	Pneumonia (0528)	1	0.2	0	1.1	0	0	0	1.4
	Rhinitis (0539)	4	0.8	0.2	2.0	1	0.4	0	2.1
Skin and appendages (100)	Eczema (0012)	0	0	0	0.7	1	0.4	0	2.1
	Seborrhea (0033)	0	0	0	0.7	1	0.4	0	2.1
	Skin disorder (0037)	0	0	0	0.7	1	0.4	0	2.1
Vision (431)	Conjunctivitis (0238)	1	0.2	0	1.1	0	0	0	1.4

Notes: D = total number of documented doses
d/% = number/percentage of doses leading to reporting of at least one report of the specified unsolicited symptom
95% CI: exact 95% confidence interval

Supplement 48: The percentage of doses with unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	**WHO Preferred term (CODE)**	**HRV D = 522**				**Placebo D = 257**			
				95% CI				**95% CI**	
		d	**%**	**L.L.**	**U.L.**	**d**	**%**	**L.L.**	**U.L.**
At least one symptom		275	52.7	48.3	57.0	128	49.8	43.5	56.1
Application site (1820)	Dermatitis contact (0049)	2	0.4	0	1.4	0	0	0	1.4
	Injection site pain (0057)	0	0	0	0.7	1*	0.4	0	2.1
Body as a whole general (1810)	Allergic reaction (0712)	1	0.2	0	1.1	0	0	0	1.4
	Allergy (1058)	1	0.2	0	1.1	0	0	0	1.4
	Crying abnormal (1162)	8	1.5	0.7	3.0	6	2.3	0.9	5.0
	Fatigue (0724)	11	2.1	1.1	3.7	5	1.9	0.6	4.5
	Fever (0725)	40	7.7	5.5	10.3	17	6.6	3.9	10.4
	Injury (9001)	1	0.2	0	1.1	2	0.8	0.1	2.8
	Pain (0730)	11	2.1	1.1	3.7	3	1.2	0.2	3.4
Cardiovascular general (1010)	Heart disorder (0504)	0	0	0	0.7	2	0.8	0.1	2.8
Central and peripheral nervous system (410)	Dysphonia (0103)	1	0.2	0	1.1	0	0	0	1.4
	Headache (0109)	1	0.2	0	1.1	0	0	0	1.4
Fetal (1500)	Hernia congenital (0885)	1	0.2	0	1.1	0	0	0	1.4

Notes: D = total number of documented doses
d/% = number/percentage of doses leading to reporting of at least one report of the specified unsolicited symptom
At least one symptom = total number of doses followed by at least one report of an unsolicited symptom, whatever the WHO Preferred terms
95% CI: exact 95% confidence interval
*Following DTP vaccination

Supplement 48 (continued): The percentage of doses with unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV D = 522				Placebo D = 257			
				95% CI				95% CI	
		d	%	L.L.	U.L.	d	%	L.L.	U.L.
Gastrointestinal system (600)	Abdominal pain (0268)	12	2.3	1.2	4	3	1.2	0.2	3.4
	Anorexia (0165)	3	0.6	0.1	1.7	0	0	0	1.4
	Appetite increased (0168)	1	0.2	0	1.1	0	0	0	1.4
	Constipation (0204)	9	1.7	0.8	3.2	2	0.8	0.1	2.8
	Diarrhea (0205)	7	1.3	0.5	2.7	2	0.8	0.1	2.8
	Dyspepsia (0279)	1	0.2	0	1.1	0	0	0	1.4
	Flatulence (0285)	18	3.4	2.1	5.4	4	1.6	0.4	3.9
	GE (0293)	2	0.4	0	1.4	0	0	0	1.4
	Gastroesophageal reflux (1149)	18	3.4	2.1	5.4	4	1.6	0.4	3.9
	Melena (0306)	1	0.2	0	1.1	2	0.8	0.1	2.8
	Stomatitis (0327)	1	0.2	0	1.1	0	0	0	1.4
	Tongue disorder (0330)	1	0.2	0	1.1	0	0	0	1.4
	Tooth ache (1376)	6	1.1	0.4	2.5	5	1.9	0.6	4.5
	Vomiting (0228)	4	0.8	0.2	2.0	2	0.8	0.1	2.8

Notes: D = total number of documented doses
d/% = number/percentage of doses leading to reporting of at least one report of the specified unsolicited symptom
95% CI: exact 95% confidence interval

Supplement 48 (continued): The percentage of doses with unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	**WHO Preferred term (CODE)**	**HRV D = 522**				**Placebo D = 257**			
				95% CI				**95% CI**	
		d	**%**	**L.L.**	**U.L.**	**d**	**%**	**L.L.**	**U.L.**
Hearing and vestibular (432)	Ear disorder nos (1255)	1	0.2	0	1.1	0	0	0	1.4
Metabolic and nutritional (800)	Growth retarded (0379)	1	0.2	0	1.1	2	0.8	0.1	2.8
	Thirst (0405)	1	0.2	0	1.1	0	0	0	1.4
Neonatal and infancy (1600)	Feeding disorder neonatal (0909)	1	0.2	0	1.1	0	0	0	1.4
Platelet bleeding and clotting (1230)	Purpura (0459)	2	0.4	0	1.4	0	0	0	1.4
Psychiatric (500)	Insomnia (0183)	5	1	0.3	2.2	2	0.8	0.1	2.8
	Nervousness (0188)	77	14.8	11.8	18.1	38	14.8	10.7	19.7
	Sleep disorder (0195)	1	0.2	0	1.1	1	0.4	0	2.1
	Somnolence (0197)	2	0.4	0	1.4	2	0.8	0.1	2.8

Notes: D = total number of documented doses
d/% = number/percentage of doses leading to reporting of at least one report of the specified unsolicited symptom
95% CI: exact 95% confidence interval

Supplement 48 (continued): The percentage of doses with unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV D = 522				Placebo D = 257			
				95% CI				95% CI	
		d	%	L.L.	U.L.	d	%	L.L.	U.L.
Resistance mechanism (1830)	Abscess (0887)	1	0.2	0	1.1	0	0	0	1.4
	Infection (0736)	2	0.4	0	1.4	0	0	0	1.4
	Infection bacterial (0738)	1	0.2	0	1.1	0	0	0	1.4
	Infection fungal (0739)	2	0.4	0	1.4	0	0	0	1.4
	Infection viral (0740)	7	1.3	0.5	2.7	4	1.6	0.4	3.9
	Moniliasis (0741)	6	1.1	0.4	2.5	0	0	0	1.4
	Otitis media (0750)	22	4.2	2.7	6.3	8	3.1	1.4	6.0
	Upper resp tract infection (0543)	27	5.2	3.4	7.4	12	4.7	2.4	8.0
Respiratory system(1100)	Asthma (1367)	1	0.2	0	1.1	0	0	0	1.4
	Bronchitis (0805)	2	0.4	0	1.4	1	0.4	0	2.1
	Coughing (0513)	27	5.2	3.4	7.4	10	3.9	1.9	7.0
	Dyspnea (0514)	2	0.4	0	1.4	0	0	0	1.4
	Laryngitis (0521)	1	0.2	0	1.1	1	0.4	0	2.1
	Pharyngitis (0523)	1	0.2	0	1.1	0	0	0	1.4
	Pneumonia (0528)	1	0.2	0	1.1	0	0	0	1.4
	Rhinitis (0539)	78	14.9	12	18.3	35	13.6	9.7	18.4

Notes: D = total number of documented doses
d/% = number/percentage of doses leading to reporting of at least one report of the specified unsolicited symptom
95% CI: exact 95% confidence interval

Supplement 48 (continued): The percentage of doses with unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)	**WHO Preferred term (CODE)**	**HRV D = 522**				**Placebo D = 257**			
				95% CI				**95% CI**	
		d	**%**	**L.L.**	**U.L.**	**d**	**%**	**L.L.**	**U.L.**
Skin and appendages (100)	Bullous eruption (0871)	0	0	0	0.7	1	0.4	0	2.1
	Eczema (0012)	9	1.7	0.8	3.2	4	1.6	0.4	3.9
	Nail disorder (0020)	1	0.2	0	1.1	0	0	0	1.4
	Pigmentation abnormal (0973)	0	0	0	0.7	1	0.4	0	2.1
	Pruritus (0024)	1	0.2	0	1.1	0	0	0	1.4
	Rash (0027)	6	1.1	0.4	2.5	2	0.8	0.1	2.8
	Rash erythematous (0028)	1	0.2	0	1.1	1	0.4	0	2.1
	Seborrhea (0033)	0	0	0	0.7	1	0.4	0	2.1
	Skin disorder (0037)	1	0.2	0	1.1	2	0.8	0.1	2.8
	Skin dry (1123)	0	0	0	0.7	1	0.4	0	2.1
Vision (431)	Conjunctivitis (0238)	22	4.2	2.7	6.3	20	7.8	4.8	11.8

Notes: D = total number of documented doses
d/% = number/percentage of doses leading to reporting of at least one report of the specified unsolicited symptom
95% CI: exact 95% confidence interval

Supplement 49: The percentage of subjects with gastrointestinal symptoms (unsolicited symptoms), from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)		**HRV N = 267**				**Placebo N = 133**			
				95% CI				**95% CI**	
	Symptom	**s**	**%**	**L.L.**	**U.L.**	**s**	**%**	**L.L.**	**U.L.**
Gastrointestinal system (600)	Any	64	24.0	19.0	29.6	20	15.0	9.4	22.3
	Related	30	11.2	7.7	15.7	5	3.8	1.2	8.6
	Grade 3	6	2.2	0.8	4.8	2	1.5	0.2	5.3

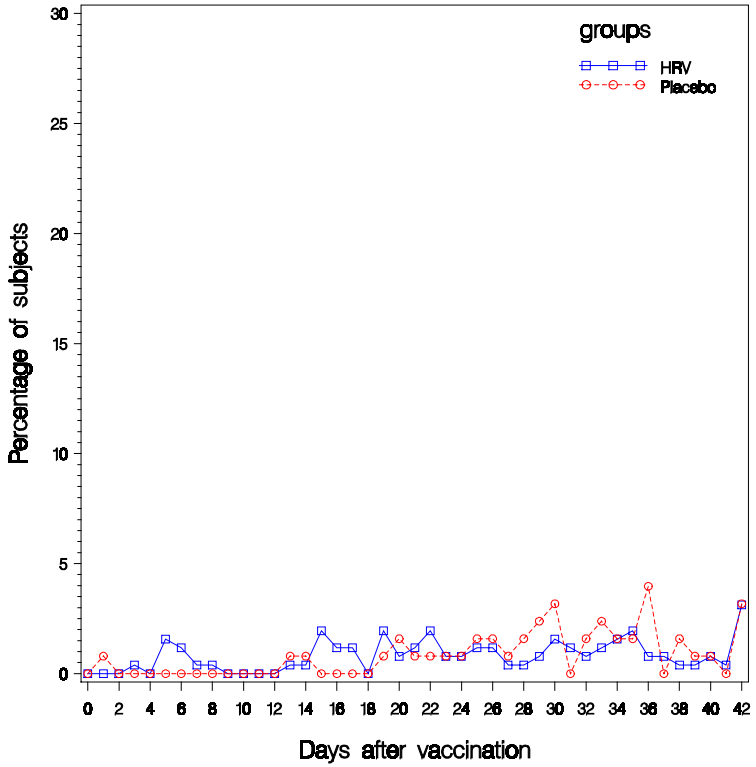
Notes: N = number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting at least once the specified unsolicited symptom
95% CI: exact 95% confidence interval

Supplement 50: The percentage of doses with gastrointestinal symptoms (unsolicited symptoms), from Day 0 to Day 42 after any vaccination (total cohort)

WHO Body System (CODE)		**HRV D = 522**				**Placebo D = 257**			
				95% CI				**95% CI**	
	Symptom	**d**	**%**	**L.L.**	**U.L.**	**d**	**%**	**L.L.**	**U.L.**
Gastrointestinal system (600)	Any	72	13.8	11.0	17.1	22	8.6	5.4	12.7
	Related	32	6.1	4.2	8.5	5	1.9	0.6	4.5
	Grade 3	6	1.1	0.4	2.5	2	0.8	0.1	2.8

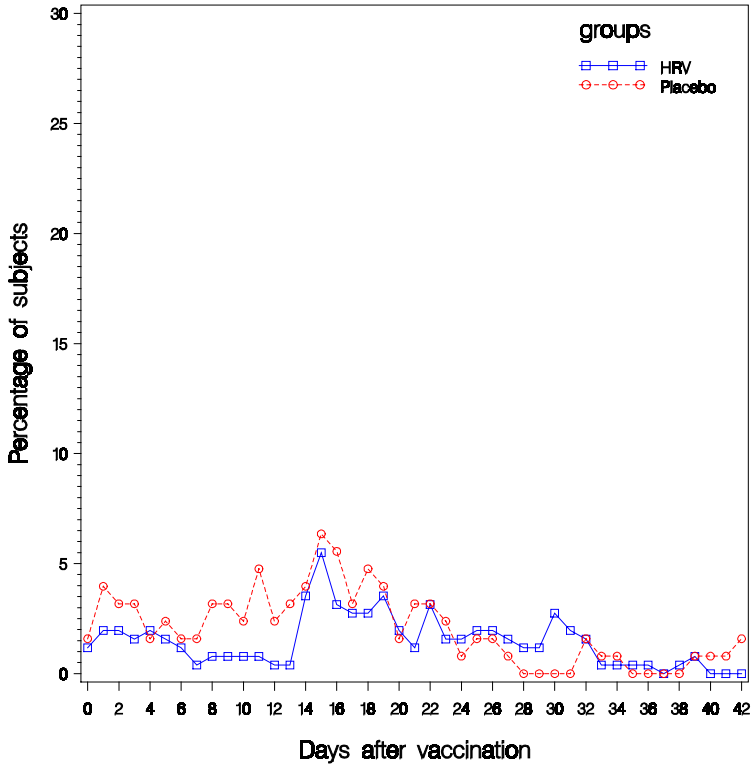
Notes: D = total number of documented doses
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI: exact 95% confidence interval

Supplement 51: Percentage of subjects who started taking antipyretic after Dose 1, by day from Day 0 to Day 42 (total cohort)



Y-axis was cut at 30%

Supplement 52: Percentage of subjects who started taking antipyretic after Dose 2, by day from Day 0 to Day 42 (total cohort)



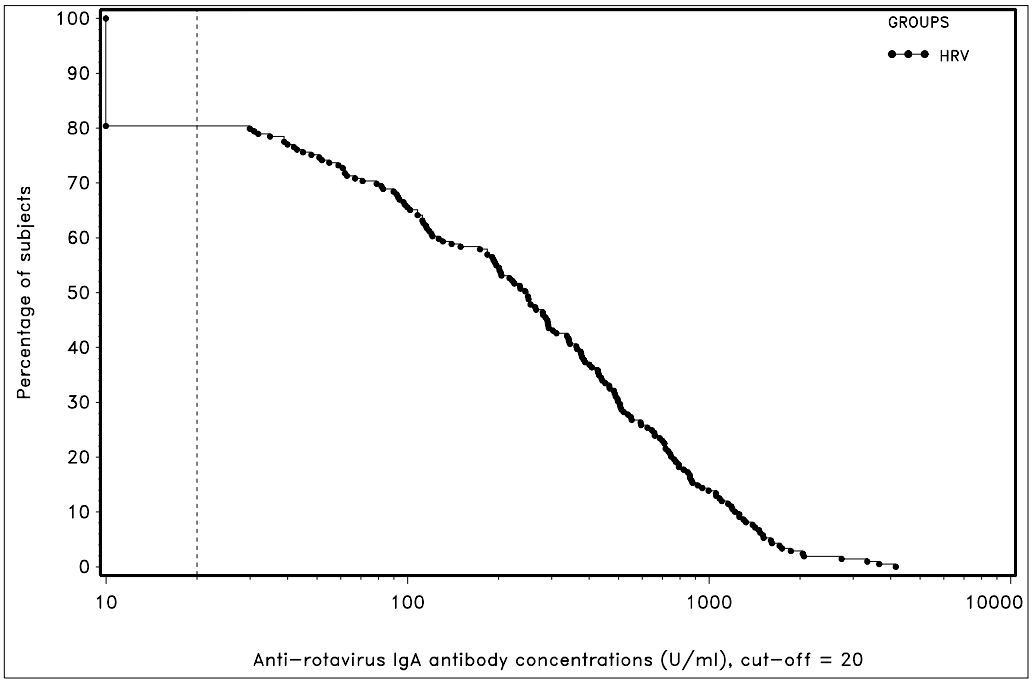
Y-axis was cut at 30%

Supplement 53: Distribution of anti-rotavirus IgA antibody concentrations (ATP immunogenicity cohort)

Group	Timing	N	≥ 20 U/ml		≥ 40 U/ml		≥ 80 U/ml		≥ 160 U/ml		≥ 320 U/ml		≥ 640 U/ml		≥ 1280 U/ml	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%
HRV	Pre	209	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	PII(M3)	209	168	80.4	162	77.5	146	69.9	122	58.4	89	42.6	53	25.4	19	9.1
	ES1	189	143	75.7	136	72.0	106	56.1	73	38.6	39	20.6	11	5.8	4	2.1
Placebo	Pre	112	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	PII(M3)	112	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	ES1	106	16	15.1	16	15.1	16	15.1	15	14.2	13	12.3	9	8.5	0	0.0

Notes: N = number of subjects with available data
n/% = number/percentage of subjects with concentration above the specified range
Pre = Pre-vaccination PII(M3) = one month after the second vaccination ES1 = end of the first RV season

Supplement 54: Reverse cumulative distribution curve for anti-rotavirus IgA antibody concentrations one month after Dose 2, in the HRV vaccine group (ATP immunogenicity cohort)



Supplement 55: Percentage of subjects in the HRV vaccine group reporting RV GE during the first efficacy follow-up period, by status of anti-rotavirus IgA antibody concentration at Visit 3 (ATP efficacy cohort)

Anti-rotavirus IgA antibody status at Visit 3	N	n	%	95%CI	
ELISA					
Negative	45	4	8.9	2.5	21.2
Positive	180	3	1.7	0.3	4.8
Unknown	20	1	5.0	0.1	24.9
RT-PCR					
Negative	45	5	11.1	3.7	24.1
Positive	180	6	3.3	1.2	7.1
Unknown	20	1	5.0	0.1	24.9

Notes:
N = number of subjects included in the HRV vaccine group with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 (Visit 3)
n/% = number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 reporting at least one RV GE episode during the first efficacy follow-up period
95%CI = exact 95%confidence intervals

Supplement 56: Anti-rotavirus IgA antibody GMC and seropositivity rates (total cohort)

Group	Timing	N	≥ 20 U/ml				GMC (IU/ml)		
					95% CI		Value	95% CI	
			n	%	L.L.	U.L.		L.L.	U.L.
HRV	Pre	265	0	0.0	0.0	1.4	<20	-	-
	PII(M3)	233	186	79.8	74.1	84.8	157.0	125.7	196.1
	ES1	224	170	75.9	69.7	81.3	81.8	67.4	99.1
Placebo	Pre	133	0	0.0	0.0	2.7	<20	-	-
	PII(M3)	122	1	0.8	0.0	4.5	<20	-	-
	ES1	119	21	17.6	11.3	25.7	20.9	15.6	28.1

Notes: N= number of subjects with available data
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval L.L. = lower limit, U.L. = upper limit
Pre = Pre-vaccination PII(M3) = one month after the second vaccination ES1 = end of the first RV season

Supplement 57: Distribution of anti-rotavirus IgA antibody concentrations (total cohort)

Group	Timing	N	≥ 20 U/ml		≥ 40 U/ml		≥ 80 U/ml		≥ 160 U/ml		≥ 320 U/ml		≥ 640 U/ml		≥ 1280 U/ml	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%
HRV	Pre	265	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	PII(M3)	233	186	79.8	178	76.4	161	69.1	133	57.1	96	41.2	58	24.9	22	9.4
	ES1	224	170	75.9	161	71.9	125	55.8	85	37.9	46	20.5	11	4.9	4	1.8
Placebo	Pre	133	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	PII(M3)	122	1	0.8	1	0.8	1	0.8	1	0.8	1	0.8	1	0.8	0	0.0
	ES1	119	21	17.6	21	17.6	21	17.6	20	16.8	18	15.1	13	10.9	1	0.8

Notes: N= number of subjects with available data
n/% = number/percentage of subjects with concentration above the specified range
Pre = Pre-vaccination PII(M3) = one month after the second vaccination ES1 = end of the first RV season

Supplement 58: Anti-rotavirus IgA antibody GMC calculated on calculated on subjects seropositive for anti-rotavirus IgA antibodies (total cohort)

			GMC (U/ml)				
				95% CI		Range	
Group	**Timing**	**N**	**Value**	**L.L.**	**U.L.**	**Min**	**Max**
HRV	PII(M3)	186	314.8	266.8	371.5	28	4161
	ES1	170	159.4	137.4	184.9	24	3211
Placebo	PII(M3)	1	668.0	-	-	668	668
	ES1	21	659.4	489.3	888.6	116	1824

Notes: N= number of subjects who were seropositive for anti-rotavirus IgA antibodies
PII(M3) = one month after the second vaccination ES1 = end of the first RV season

Appendix A: Clintrial Eligibility Codes

Elimination from ATP analysis of safety, immunogenicity and efficacy

1010 Subject or vaccine number not allocated
HRV vaccine or placebo not administered at all
No subject allocated to the randomized number

1030 Study vaccine dose not administered but subject number allocated
HRV vaccine or placebo not administered at all

1040 Administration of vaccine(s) forbidden in the protocol

1050 Randomization failure
Replacement vial used in double-blind studies in with replacement dose are unique whatever the vaccine group
Wrong vaccine vial given
Subject number not in the randomization list and not requested by the sponsor (extra subject)

1060 Randomization code broken at the investigator site (for double-blind studies)

1070 HRV or placebo dose not administered according to protocol

1080 Essential data missing
Date of vaccination unknown
No information on solicited or unsolicited symptoms available: all is missing

1500 Others
Initially positive for rotavirus on the day of dose 1

Elimination from ATP analysis of immunogenicity

2010 Protocol violation (any inclusion/exclusion criteria not met at study entry)
Ex : Demographics - Too young
Too old
Unknown age
Underlying medical condition forbidden by the protocol at screening / Medical history

2040 Administration of any medication forbidden by the protocol

2050 Underlying medical condition forbidden by the protocol during the study

2060 Concomitant infection by rotavirus which may influence immune response

2070 Concomitant infection not related to the vaccine which may influence immune response

2080 Non compliance with vaccination schedule (including wrong and unknown dates)
Not assigned if code 2100 or 2110 has been assigned

2090 Non compliance with blood sample schedule (including wrong and unknown dates)
Not assigned if code 2100 or 2110 has been assigned

2100 Essential serological data missing
Essential blood sample lost
Essential blood sample unable to test (hemolysis, insufficient volume, ...)
Essential blood sample not done
Absence of parallelism

2110 Essential serological data temporarily missing because of not yet tested (interim analysis)

2120 Obvious incoherence, abnormal serology evolution or error in data (incoherence between CRF and results)
Wrong labeling in BS

2130 Subject not planned in the protocol to be bled for their all blood sampling visits (and effectively not bled)

2500 Others

Elimination from ATP analysis of Efficacy

3010 At least one study vaccine dose not administered

3020 Subjects not entered into the surveillance period

3030 Concomitant infection by rotavirus up to 2 weeks after dose 2 which may influence efficacy response

Appendix B: Mathematical details about the computation of the 95%CI for vaccine efficacy*

The Vaccine Efficacy (VE) can be estimated by:

$$VE = 1 - \frac{n1/N1}{n2/N2} = 1 - \frac{n1}{r * n2}$$

where n1 = number of cases in the vaccine group
N1 = number of subjects in the vaccine group
n1 = number of cases in the placebo group
N2 = number of subjects in the placebo group
r = $\frac{N1}{N2}$

Conditionally to the total number of cases n = n1+ n2 and r, let *p* denote the proportion of cases in the vaccine group,

$$VE = 1 - \frac{n1}{n} * \frac{n}{r * (n - n1)} = 1 - p * \frac{1}{r * (1 - p)} = 1 - \frac{p}{r * (1 - p)}$$

where $p = n1/n$ is binomially distributed

There is therefore a monotonic link between VE, the true vaccine efficacy, and p, the true proportion of subjects in the vaccine group among the total cases in the two groups.

95%CI for vaccine efficacy can then be derived from the exact 95% CI from p.

* V. Dragalin, V. Fedorov and B. Cheuvart. Statistical approaches to establishing vaccine safety. Statistics in medicine 2002; 21:877-893

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

CONFIDENTIAL

Annex Report for Clinical Trial 444563/004 (rota-004)

Title: A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants approximately 2 months of age and previously uninfected with HRV.

Study vaccines:	GlaxoSmithKline Biologicals' live attenuated human rotavirus vaccine.
CPMS Study No.:	444563/004 (rota-004)
Indication:	Two oral doses at two months interval to healthy infants, 2 months (6–12 weeks) of age at the time of Dose 1.
Principal Investigator:	Prof. [redacted]
Date of First Visit:	August 21, 2000
Data lock point for final analysis at the end of 1st rotavirus season:	July 11, 2001
Date of Last Visit:	26 June, 2002
Coordinating Author:	[redacted] Scientific Writer
Contributing authors:	[redacted] Biometrician Clinical Development Manager [redacted] Central Study Coordinator

The trial was performed according to the Good Clinical Practice guidelines in operation at the time of the initiation of the trial.

Final Report Date: April 30, 2003

Annex Report Date: November 14, 2003

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

CONFIDENTIAL

This annex report provides results from the end of the first rotavirus season post-vaccination until the end of the study at the end of the second rotavirus season post-vaccination and efficacy analyses over the two consecutive rotavirus seasons.

Synopsis of Annex Report for Clinical Trial 444563/004 (rota-004)

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Title of the study: A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GSK Biologicals' oral live attenuated human rotavirus (HRV) vaccine in healthy infants approximately 2 months of age and previously uninfected with HRV.

Principal Investigator: Prof. [redacted] Finland

Study sites: The trial was conducted at six sites in Finland.

Publications:

- Efficacy of the oral HRV vaccine in healthy infants during two consecutive rotavirus seasons. Poster presented at European Society for Pediatric Infectious Diseases (ESPID), Sicily, April 9–11, 2003.
- Efficacy of oral human rotavirus vaccine in infants against acute rotavirus gastroenteritis in the community determined with rotavirus antigen detection by EIA and rotavirus RT-PCR as end points. Oral communication accepted for presentation at European Society for Clinical Virology (ESCV), Lyon, France, August 24–27, 2003.
- Randomized placebo-controlled efficacy evaluation of RIX4414 live attenuated human rotavirus vaccine in healthy infants. Vesikari T, Karvonen A, Puustinen L, Szakal D, Zeng S-Q, Delem A and De Vos B. Submitted to BMJ.

Study period:	Date of first visit: August 21, 2000 Data lock point for final analysis at the end of the first efficacy follow-up period: July 11, 2001 Date of last visit: June 26, 2002	**Clinical phase:** IIb

Note: This annex report only presents study objectives, criteria for evaluation, endpoints and results pertaining to the annex analysis.
Actual viral concentration contained in GSK Biologicals' HRV vaccine (i.e. $10^{4.7}$ ffu) is mentioned.

Objectives:
Only objectives pertaining to the annex analysis of this study are mentioned below.
Secondary:
Efficacy

- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent severe RV GE during the period starting from the end of the first RV season following vaccination until the end of the second RV season following vaccination.
- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent any and severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.
- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent any and severe GE of any etiology (RV or not) during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

- To assess if the RV detection method (ELISA *versus* RT-PCR) modifies vaccine efficacy.
- To characterize the G type of the wild RV strain by RT-PCR.

Safety

- To assess the safety of two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine *versus* placebo.

Immunogenicity

- To assess the immunogenicity (serum IgA antibody levels) of two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine.

Methodology:
Study design: Double-blind, randomized, placebo-controlled, self-contained study with two parallel groups with unbalanced allocation (2:1 for vaccine:placebo).

Number of subjects:

Enrolled: 405 (270 in HRV group and 135 in placebo group)

Completed until Visit 4: 372 (249 in HRV group and 123 in placebo group)

Completed until Visit 5: 363 (244 in HRV group and 119 in placebo group)

Analyzed for efficacy during first efficacy follow-up period:
Total efficacy cohort: 381 (255 in HRV group and 126 in placebo group)
ATP cohort: 368 (245 in HRV group and 123 in placebo group)

Analyzed for efficacy during second efficacy follow-up period:
Total efficacy cohort: 374 (251 in HRV group and 123 in placebo group)
ATP cohort: 361 (241 in HRV group and 120 in placebo group)

Analyzed for efficacy over two consecutive efficacy follow-up periods:
Total efficacy cohort: 381 (255 in HRV group and 126 in placebo group)
ATP cohort: 368 (245 in HRV group and 123 in placebo group)

Analyzed for immunogenicity:
Total immunogenicity cohort: 404 (269 in HRV group and 135 in placebo group)

Diagnosis and criteria for inclusion: Healthy infants, born after a normal gestation period of 36–42 weeks, 6–12 weeks of age at the time of the first dose of the study vaccination course, free of obvious health problems as established by medical history and clinical examination before entering into the study, and with written informed consent obtained from parents or guardians of the subject.

Test product, dose, mode of administration, lot numbers:

- Each reconstituted dose (1 ml) of GSK Biologicals' HRV vaccine consisted of $10^{4.7}$ ffu of HRV strain, RIX4414 derived from the 89-12 HRV vaccine strain, 9 mg sucrose, 18 mg dextran, 13.5 mg sorbitol and 9 mg amino acids. Lot number DRVC005A46 was used.
  Lot 00C16/1000 was used for the diluent (calcium carbonate 60 mg/ml and xanthane 0.25 % in water for injection).

Mode of administration: Lyophilized HRV vaccine was reconstituted with the supplied diluent and the resuspended product was administered as a single oral dose.

Reference therapy, dose and mode of administration, lot number:

- Each reconstituted dose (1 ml) of GSK Biologicals' placebo consisted of 9 mg sucrose, 18 mg dextran, 13.5 mg sorbitol and 9 mg amino acids. Lot DRVC006A46PL was used.
  Lot 00C16/1000 was used for the diluent (calcium carbonate 60 mg/ml and xanthane 0.25 % in water for injection).

Mode of administration: Lyophilized placebo was reconstituted with the supplied diluent and the resuspended product was administered as a single oral dose.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Duration of treatment: The intended duration of the study, per subject, was approximately 2 years (approximately 9 months of follow-up until the end of the first RV season and one year follow-up until the end of the second RV season post-vaccination).

Criteria for evaluation:

Efficacy: Recording of rectal temperature, number of vomiting episodes, number of looser than normal stools passed by the subject, treatment administered and any dehydration during each suspected episode of GE occurring from the end of the first RV season until the end of the second RV season following vaccination. Collection of stool samples during each GE episode for RV detection. Episodes were counted as distinct events only if there were 5 or more symptom-free days between the episodes. A 20-point scale was used to assess the severity of each GE episode (Ruuska T and Vesikari T, Scand J Infect Dis 1990;22:259-267). A score of < 7 was prospectively defined as mild, a score of 7–10 was prospectively defined as moderate and a score ≥ 11 was prospectively defined as severe (Joensuu J *et al*, Lancet 1997;350:1205-9).

Measurement of serum concentration of RV specific IgA antibodies at the end of second RV season (at Visit 5) to detect asymptomatic RV infection. Seroconversion or ≥ 4-fold rise in anti-rotavirus antibody IgA concentration between one month post Dose 2 and end of the season time point was considered as serological evidence of asymptomatic RV infection.

Secondary endpoints:

- Occurrence of severe RV GE during the period starting from the end of the first RV season until the end of the second RV season following vaccination as detected by ELISA and as detected by RT-PCR in stool samples.
- Occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination as detected by ELISA and as detected by RT-PCR in stool samples.
- Occurrence of any and severe GE of any etiology (RV or not) during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.
- Occurrence of asymptomatic RV infections during the period starting from 1 month after Dose 2 until the end of the second RV season following vaccination.
- G type of the wild RV strain by RT-PCR.

Safety: Recording of serious adverse events (SAE) after Visit 4 until Visit 5.

Secondary endpoints:

- Occurrence of serious adverse events after Visit 4 until Visit 5.

Immunogenicity*:* Measurement of serum concentration of RV specific IgA antibodies in all subjects.

Secondary endpoint: Serum rotavirus IgA antibody concentration at each blood sampling timepoint.

Statistical methods:

Efficacy: Efficacy analysis was performed on the According to Protocol (ATP) cohort (primary analysis) and on the total cohort. A global overview of the number of GE episodes of any etiology (RV or not) and RV GE episodes reported by the subjects during the second efficacy follow-up period and from 2 weeks after Dose 2 until end of the second efficacy follow-up period after vaccination was provided for each group. The percentage of subjects reporting RV GE (any and severe intensity) during the second efficacy follow-up period and over two consecutive efficacy follow-up periods following vaccination were calculated by group with its 95% Confidence Interval (CI).

444563/004 Synopsis page 3 of 6

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

The percentage of subjects with an asymptomatic RV infection from approximately one month after Dose 2 until the end of the second efficacy follow-up period was calculated by group with its 95% CI. The percentage of subjects with any and severe GE of any etiology (RV or not) from 2 weeks after Dose 2 until the end of the second efficacy follow-up period was calculated by group with its 95% CI. Two-sided Fisher's exact test (significance level of α=0.05) was used to compare these percentages between groups. The efficacy rate (overall and by type) of the HRV vaccine relative to the placebo was calculated with its 95% CI against RV GE (any and severe intensity) during the second RV season and over two consecutive efficacy follow-up periods. The efficacy rate against asymptomatic RV infection occurring from approximately one month after Dose 2 until the end of the second RV season following vaccination was calculated. The efficacy rate against GE of any etiology (RV or not), with any and severe intensity, occurring from two weeks after Dose 2 until the end of the second RV season following vaccination was also calculated.

Safety and reactogenicity:
The Serious Adverse Events (SAEs) and discontinuations due to adverse events after Visit 4 until Visit 5 were described.

Immunogenicity: Immunogenicity analysis was performed only on the total cohort. Geometric Mean Concentration (GMC) and seropositivity rates at all blood sampling timepoints were calculated with their 95% CI for each group. The distribution of IgA antibody concentrations at Visit 5 were displayed using reverse cumulative curves.

Efficacy results:
Efficacy during the second efficacy follow-up period after vaccination: The second efficacy follow-up period started on June 2, 2001 and ended at the end of the second RV season on June 1, 2002. A statistically significant decrease in the percentage of subjects reporting any and severe RV GE by ELISA during the second efficacy follow-up period was detected in the HRV vaccine group as compared to the placebo group ($p < 0.05$, two-sided Fisher's exact test).
The percentages of subjects reporting RV GE (any and severe intensity) when ELISA was used to detect RV and vaccine efficacy during the second efficacy follow-up period for the ATP efficacy cohort were as follows:

Group	N	Rate			Vaccine efficacy			p-value
		%	95% CI LL	95% CI UL	%	95% CI LL	95% CI UL	
Any RV GE								
HRV	241	2.9	1.2	5.9	71.0	20.0	90.3	0.010
Placebo	120	10.0	5.3	16.8				
Severe RV GE								
HRV	241	0.8	0.1	3.0	83.4	7.2	98.4	0.018
Placebo	120	5.0	1.9	10.6				

N = number of subjects included in each group
Rate = percentage of subjects reporting at least one specific RV GE episode in each group
95% CI = 95% confidence interval; L.L. = lower limit, U.L. = upper limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

444563/004 Synopsis page 4 of 6

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

When RT-PCR was used for detection of RV, vaccine efficacy against any RV GE was 70.1% (95% CI, 9.3–91.1) and vaccine efficacy against severe RV GE was 83.4% (95% CI, 7.2–98.4). A statistically significant decrease in the percentage of subjects reporting any and severe RV GE by RT-PCR during the second efficacy follow-up period was detected in the HRV vaccine group as compared to the placebo group ($p < 0.05$, two-sided Fisher's exact test).
G1 strain was the predominant strain causing RV GE episodes in both groups during the second efficacy follow-up period.
One subject from the HRV vaccine group was hospitalized due to RV GE of G9 type and with a score of 15 during the second efficacy follow-up period.

Efficacy over two consecutive efficacy follow-up periods after vaccination: The combined efficacy follow-up period started 2 weeks after Dose 2 and ended at the end of the second RV season on June 1, 2002. A statistically significant decrease in the percentage of subjects reporting any and severe RV GE by ELISA over two consecutive years after vaccination was detected in the HRV vaccine group as compared to the placebo group ($p < 0.05$, two-sided Fisher's exact test).
The percentages of subjects reporting RV GE (any and severe intensity) when ELISA was used to detect RV and vaccine efficacy during this period for the ATP efficacy cohort were as follows:

Group	N	Rate			Vaccine efficacy			p-value
		%	95% CI LL	95% CI UL	%	95% CI LL	95% CI UL	
Any RV GE								
HRV	245	6.1	3.5	9.9	68.6	37.7	84.7	<0.001
Placebo	123	19.5	12.9	27.6				
Severe RV GE								
HRV	245	1.2	0.3	3.5	84.9	41.5	97.3	0.001
Placebo	123	8.1	4.0	14.4				

N = number of subjects included in each group
Rate = percentage of subjects reporting at least one RV GE episode in each group
95% CI = 95% confidence interval; L.L. = lower limit, U.L. = upper limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

When RT-PCR was used for detection of RV, vaccine efficacy against any RV GE was 61.2% (95% CI, 23.5–80.7) and vaccine efficacy against severe RV GE was 84.9% (95% CI, 41.5–97.3). A statistically significant decrease in the percentage of subjects reporting any and severe RV GE by RT-PCR over two consecutive efficacy follow-up periods after vaccination was detected in the HRV vaccine group as compared to the placebo group ($p < 0.05$, two-sided Fisher's exact test).
Vaccine efficacy against occurrence of asymptomatic RV infection during the period starting from one month after Dose 2 until the end of the second RV season following vaccination was 82.1% (95% CI, 37.8–95.9) by ELISA and 83.2% (95% CI, 43.4–96.1) by RT-PCR. A statistically significant decrease in the percentage of subjects reporting asymptomatic RV infection was detected in the HRV vaccine group as compared to the placebo group ($p < 0.05$, two-sided Fisher's exact test).
The proportion of subjects reporting any GE of any etiology (RV or not) from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period was similar between the groups: 66.1% in the HRV vaccine group and 65.0% in the placebo group. The percentage of subjects reporting severe GE of any etiology (RV or not) was lower, although not statistically significant, in the HRV vaccine group as compared to the placebo group and vaccine efficacy of 45% (95% CI, –37.0–77.9) was observed.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

ELISA or RT-PCR tests were repeated for four subjects (one had RV GE during the first efficacy follow-up period and three had RV GE during the second efficacy follow-up period) since there were inconsistencies in the results for these subjects. RT-PCR test was done for two subjects (one had RV GE during the first efficacy follow-up period and one had RV GE during the second efficacy follow-up period) with previous missing results.
Calculations pertaining to the main objectives of the study, i.e. vaccine efficacy, were redone and the results of the reanalysis with the corrected test results are presented in Erratum dated November 13, 2003. Although the efficacy estimates were slightly higher after the reanalysis, the changes did not alter the study conclusions.

Safety Results:
Twenty subjects (13 in the HRV vaccine group and 7 in the placebo group) reported at least one SAE after Visit 4 until Visit 5. None of the SAEs were assessed as related to study vaccination.

Immunogenicity Results:
At the end of the second RV efficacy follow-up period, anti-rotavirus IgA antibodies were still present in 67.2% (95% CI, 60.8–73.3) of subjects in the HRV vaccine group.

Conclusions:

- GSK Biologicals' HRV vaccine was efficacious in decreasing the incidence of any and severe RV GE relative to the placebo during the period starting from the end of the first RV season following vaccination until the end of the second RV season following vaccination.
- GSK Biologicals' HRV vaccine was efficacious in decreasing the incidence of any and severe RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.
- During the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination, GE of any etiology (RV or not) occurred at similar rates in the HRV vaccine and placebo groups. However, the percentage of subjects reporting severe GE of any etiology was lower, although not statistically significant, in the HRV vaccine group as compared to the placebo group.
- GSK Biologicals' HRV vaccine was efficacious in decreasing the incidence of asymptomatic RV infections relative to the placebo during the period starting from one month after Dose 2 until the end of the second RV season following vaccination.
- The G1 type was predominant among the wild type RV circulating during the second RV season following vaccination.
- The method (ELISA *versus* RT-PCR) used for detection of RV did not appear to modify the estimate of vaccine efficacy against any and severe RV GE during the period starting from the end of the first RV season following vaccination until the end of the second RV season following vaccination and during the entire follow-up period (from 2 weeks after Dose 2 until the end of the second RV season following vaccination).
- GSK Biologicals' HRV vaccine was safe and no vaccination-related SAEs were reported after Visit 4 until Visit 5.

Date of report: November 14, 2003

444563/004 Synopsis page 6 of 6

CONTENTS: TEXT

SYNOPSIS OF ANNEX REPORT FOR CLINICAL TRIAL 444563/004 (ROTA-004)..... 3

1 INTRODUCTION/RATIONALE 21

2 STUDY OBJECTIVES 22

2.1 SECONDARY OBJECTIVES 22

3 METHODOLOGY 23

3.1 STUDY DESIGN 23
3.2 INVESTIGATORS AND TRIAL CENTERS 23
3.3 ETHICS 23
3.3.1 Protocol amendments/modifications 23
3.4 SELECTION OF STUDY POPULATION 23
3.5 STUDY VACCINES AND ADMINISTRATION 23
3.6 TREATMENT ALLOCATION AND RANDOMIZATION 23
3.7 BLINDING 24
3.8 STUDY PROCEDURES 24
3.9 SUBJECT COMPLETION AND DROP-OUT 24
3.10 ASSESSMENT OF EFFICACY VARIABLES 25
3.10.1 Laboratory assays and timepoints 25
3.11 ASSESSMENT OF SAFETY VARIABLES 25
3.11.1 Pregnancy 26
3.11.2 Prior and concomitant medication 26
3.12 ASSESSMENT OF IMMUNOGENICITY VARIABLES 26
3.12.1 Laboratory assays and timepoints 26
3.13 DATA QUALITY ASSURANCE 26
3.14 STATISTICAL METHODS 27
3.14.1 Secondary endpoints 27
3.14.2 Determination of sample size 28
3.14.3 Study cohorts/data sets analyzed 28
3.14.4 Analysis of demographics 29
3.14.5 Analysis of efficacy 29
3.14.6 Analysis of safety 31
3.14.7 Analysis of immunogenicity 31
3.15 INTERIM ANALYSIS 32
3.16 ANNEX ANALYSIS 32
3.17 CHANGES IN CONDUCT OF THE STUDY/PLANNED ANALYSES 32

4 STUDY POPULATION 33

4.1 STUDY DATES 33
4.2 SUBJECT ELIGIBILITY AND ATTRITION FROM STUDY 34
4.2.1 Number and distribution of subjects 34
4.2.2 Study completion and drop-out 34
4.2.3 Eligibility for analysis 35
4.2.4 Compliance with protocol specified procedures 36
4.3 DEMOGRAPHIC CHARACTERISTICS 37

5 ANALYSIS OF EFFICACY 37

5.1 ANALYSIS OF EFFICACY DURING THE SECOND EFFICACY FOLLOW-UP PERIOD AFTER VACCINATION 37

5.1.1 According to protocol analysis *37*
5.1.2 Analysis of total cohort *43*
5.2 ANALYSIS OF EFFICACY OVER TWO CONSECUTIVE EFFICACY FOLLOW-UP PERIODS AFTER VACCINATION 43
5.2.1 According to protocol analysis *43*
5.2.2 Analysis of total cohort *51*

6 ANALYSIS OF SAFETY 51

6.1 SERIOUS ADVERSE EVENTS 51
6.2 NON-SERIOUS ADVERSE EVENTS 53

7 ANALYSIS OF IMMUNOGENICITY 54

7.1 DATA SETS ANALYZED 54
7.2 TOTAL COHORT ANALYSIS 54
7.2.1 Anti- rotavirus IgA antibody response *54*

8 DISCUSSION 57

9 OVERALL CONCLUSIONS 58

10 REFERENCES. 59

CONTENTS: REPORT TABLES

TABLE 1: COUNTS OF SUBJECTS ENROLLED, COMPLETED VISIT 5, DROPPED OUT AND REASON FOR DROP-OUT (TOTAL COHORT) 34
TABLE 2: NUMBER OF SUBJECTS ENROLLED INTO THE STUDY AS WELL AS THE NUMBER OF SUBJECTS EXCLUDED FROM ATP ANALYSES WITH REASONS FOR EXCLUSION 36
TABLE 3: NUMBER OF GE EPISODES AND RV GE EPISODES REPORTED DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY SEVERITY (ATP EFFICACY COHORT) 39
TABLE 4: PERCENTAGE OF SUBJECTS WITH RV GE EPISODES REPORTED DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY RV G TYPE (ATP EFFICACY COHORT) 39
TABLE 5: PERCENTAGE OF SUBJECTS REPORTING RV GE (ANY AND SEVERE INTENSITY) AND EFFICACY OF THE VACCINE AS MEASURED BY ELISA DURING THE SECOND EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT) 41
TABLE 6: PERCENTAGE OF SUBJECTS REPORTING RV GE (ANY AND SEVERE INTENSITY) AND EFFICACY OF THE VACCINE AS MEASURED BY RT-PCR DURING THE SECOND EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT) 42
TABLE 7: NUMBER OF GE EPISODES AND RV GE EPISODES REPORTED FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD, BY SEVERITY (ATP EFFICACY COHORT) 45
TABLE 8: PERCENTAGE OF SUBJECTS WITH RV GE EPISODES REPORTED FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD, BY RV G TYPE (ATP EFFICACY COHORT) 46
TABLE 9: PERCENTAGE OF SUBJECTS REPORTING RV GE (ANY AND SEVERE INTENSITY) AND EFFICACY OF THE VACCINE AS MEASURED BY ELISA FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT) 47
TABLE 10: PERCENTAGE OF SUBJECTS REPORTING RV GE (ANY AND SEVERE INTENSITY) AND EFFICACY OF THE VACCINE AS MEASURED BY RT-PCR FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT) 48
TABLE 11: PERCENTAGE OF SUBJECTS REPORTING ANY AND SEVERE GE AND EFFICACY OF THE VACCINE FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT) 49
TABLE 12: PERCENTAGE OF SUBJECTS REPORTING ASYMPTOMATIC RV INFECTION AND EFFICACY OF THE VACCINE FROM ONE MONTH AFTER DOSE 2 UP TO THE SECOND RV SEASON TIME POINT (ATP EFFICACY COHORT) 50
TABLE 13: SUBJECTS WITH SERIOUS ADVERSE EVENTS REPORTED AFTER VISIT 4 UNTIL VISIT 5 52
TABLE 14: ANTI-ROTAVIRUS IGA ANTIBODY GMCS AND SEROPOSITIVITY RATES BY ELISA (TOTAL IMMUNOGENICITY COHORT) 55
TABLE 15: ANTI-ROTAVIRUS IGA ANTIBODY GMCS CALCULATED ON SUBJECTS SEROPOSITIVE FOR ANTI-ROTAVIRUS IGA ANTIBODIES (TOTAL IMMUNOGENICITY COHORT) 56

CONTENTS: SUPPLEMENTS

SUPPLEMENT 1: DURATION (IN YEARS) OF THE FOLLOW-UP PERIODS FOR THE SECOND EFFICACY PERIOD (ATP EFFICACY COHORT) 60
SUPPLEMENT 2: NUMBER AND PERCENTAGE OF SUBJECTS WHO REPORTED GE EPISODES AND RV GE EPISODES DURING THE SECOND EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT) 61
SUPPLEMENT 3: CHARACTERISTICS OF RV GE EPISODES REPORTED DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY ELISA (ATP EFFICACY COHORT) 62
SUPPLEMENT 4: CHARACTERISTICS OF RV GE EPISODES REPORTED DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY RT-PCR (ATP EFFICACY COHORT) 63
SUPPLEMENT 5: PERCENTAGE OF SUBJECTS REPORTING RV GE (ANY INTENSITY) AND EFFICACY OF THE VACCINE DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY TYPE (ATP EFFICACY COHORT) 64
SUPPLEMENT 6: PERCENTAGE OF SUBJECTS REPORTING SEVERE RV GE AND EFFICACY OF THE VACCINE DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY TYPE (ATP EFFICACY COHORT) 65
SUPPLEMENT 7: PERCENTAGE OF SUBJECTS HOSPITALIZED DUE TO ANY GE AND EFFICACY OF THE VACCINE DURING THE SECOND EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT) 66
SUPPLEMENT 8: PERCENTAGE OF SUBJECTS IN THE HRV VACCINE GROUP REPORTING RV GE DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY STATUS OF ANTI-ROTAVIRUS IGA ANTIBODY CONCENTRATION AT VISIT 3 (ATP EFFICACY COHORT) 67
SUPPLEMENT 9: NUMBER AND PERCENTAGE OF SUBJECTS WHO REPORTED GE EPISODE(S) DURING THE SECOND EFFICACY FOLLOW-UP PERIOD (TOTAL EFFICACY COHORT) 68
SUPPLEMENT 10: NUMBER OF ANY GE EPISODES AND RV GE EPISODES REPORTED DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY SEVERITY (TOTAL EFFICACY COHORT) 69
SUPPLEMENT 11: PERCENTAGE OF SUBJECTS WITH RV GE EPISODES REPORTED DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY TYPE (TOTAL EFFICACY COHORT) 70
SUPPLEMENT 12: CHARACTERISTICS OF RV GE EPISODES REPORTED DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY ELISA (TOTAL EFFICACY COHORT) 71
SUPPLEMENT 13: CHARACTERISTICS OF RV GE EPISODES REPORTED DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY RT-PCR (TOTAL EFFICACY COHORT) 72
SUPPLEMENT 14: DURATION (IN YEARS) OF THE FOLLOW-UP PERIODS FOR THE SECOND EFFICACY PERIOD (TOTAL EFFICACY COHORT) 73
SUPPLEMENT 15: PERCENTAGE OF SUBJECTS REPORTING RV GE AND EFFICACY OF THE VACCINE AS MEASURED BY ELISA DURING THE SECOND EFFICACY FOLLOW-UP PERIOD (TOTAL EFFICACY COHORT) 74
SUPPLEMENT 16: PERCENTAGE OF SUBJECTS REPORTING SEVERE RV GE AND EFFICACY OF THE VACCINE AS MEASURED BY RT-PCR DURING THE SECOND EFFICACY FOLLOW-UP PERIOD (TOTAL EFFICACY COHORT) 75

SUPPLEMENT 17: PERCENTAGE OF SUBJECTS REPORTING RV GE (ANY INTENSITY) AND EFFICACY OF THE VACCINE DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY TYPE (TOTAL EFFICACY COHORT) 76
SUPPLEMENT 18: PERCENTAGE OF SUBJECTS REPORTING SEVERE RV GE AND EFFICACY OF THE VACCINE DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY TYPE (TOTAL EFFICACY COHORT) 77
SUPPLEMENT 19: PERCENTAGE OF SUBJECTS HOSPITALIZED DUE TO ANY GE AND EFFICACY OF THE VACCINE DURING THE SECOND EFFICACY FOLLOW-UP PERIOD (TOTAL EFFICACY COHORT) 78
SUPPLEMENT 20: PERCENTAGE OF SUBJECTS IN THE HRV GROUP REPORTING RV GE DURING THE SECOND EFFICACY FOLLOW-UP PERIOD, BY STATUS OF ANTI-ROTAVIRUS IGA ANTIBODY CONCENTRATION AT VISIT 3 (TOTAL EFFICACY COHORT) 79
SUPPLEMENT 21: DURATION (IN YEARS) OF THE FOLLOW-UP PERIODS FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT)..... 80
SUPPLEMENT 22: NUMBER AND PERCENTAGE OF SUBJECTS WHO REPORTED GE EPISODES AND RV GE EPISODES FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT) 81
SUPPLEMENT 23: CHARACTERISTICS OF RV GE EPISODES REPORTED FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD, BY ELISA (ATP EFFICACY COHORT) 82
SUPPLEMENT 24: CHARACTERISTICS OF RV GE EPISODES REPORTED FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT)..... 83
SUPPLEMENT 25: PERCENTAGE OF SUBJECTS REPORTING RV GE (ANY INTENSITY) AND EFFICACY OF THE VACCINE FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD, BY TYPE (ATP EFFICACY COHORT) 84
SUPPLEMENT 26: PERCENTAGE OF SUBJECTS REPORTING SEVERE RV GE AND EFFICACY OF THE VACCINE FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD, BY TYPE (ATP EFFICACY COHORT) 85
SUPPLEMENT 27: PERCENTAGE OF SUBJECTS HOSPITALIZED DUE TO ANY GE AND EFFICACY OF THE VACCINE FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD (ATP EFFICACY COHORT) 86
SUPPLEMENT 28: PERCENTAGE OF SUBJECTS IN THE HRV VACCINE GROUP REPORTING RV GE FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD, BY STATUS OF ANTI-ROTAVIRUS IGA ANTIBODY CONCENTRATION AT VISIT 3 (ATP EFFICACY COHORT) 87
SUPPLEMENT 29: NUMBER AND PERCENTAGE OF SUBJECTS WHO REPORTED GE EPISODE(S) FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD (TOTAL EFFICACY COHORT) 88
SUPPLEMENT 30: NUMBER OF ANY GE EPISODES AND RV GE EPISODES REPORTED FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD, BY SEVERITY (TOTAL EFFICACY COHORT) 89

SUPPLEMENT 31: PERCENTAGE OF SUBJECTS WITH RV GE EPISODES REPORTED FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD, BY TYPE (TOTAL EFFICACY COHORT) 90
SUPPLEMENT 32: CHARACTERISTICS OF RV GE EPISODES REPORTED FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD, BY ELISA (TOTAL EFFICACY COHORT) 91
SUPPLEMENT 33: CHARACTERISTICS OF RV GE EPISODES REPORTED FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD, BY RT-PCR (TOTAL EFFICACY COHORT) 92
SUPPLEMENT 34: DURATION (IN YEARS) OF THE FOLLOW-UP PERIODS FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD (TOTAL EFFICACY COHORT) ... 93
SUPPLEMENT 35: PERCENTAGE OF SUBJECTS REPORTING RV GE AND EFFICACY OF THE VACCINE AS MEASURED BY ELISA FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD (TOTAL EFFICACY COHORT) 94
SUPPLEMENT 36: PERCENTAGE OF SUBJECTS REPORTING SEVERE RV GE AND EFFICACY OF THE VACCINE AS MEASURED BY RT-PCR FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD (TOTAL EFFICACY COHORT) 95
SUPPLEMENT 37: PERCENTAGE OF SUBJECTS REPORTING RV GE (ANY INTENSITY) AND EFFICACY OF THE VACCINE FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD, BY TYPE (TOTAL EFFICACY COHORT) 96
SUPPLEMENT 38: PERCENTAGE OF SUBJECTS REPORTING SEVERE RV GE AND EFFICACY OF THE VACCINE FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD, BY TYPE (TOTAL EFFICACY COHORT) 97
SUPPLEMENT 39: PERCENTAGE OF SUBJECTS HOSPITALIZED DUE TO ANY GE AND EFFICACY OF THE VACCINE FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD (TOTAL EFFICACY COHORT) 98
SUPPLEMENT 40: PERCENTAGE OF SUBJECTS REPORTING ASYMPTOMATIC RV INFECTION AND EFFICACY OF THE VACCINE FROM VISIT 3 UP TO VISIT 5 (END OF THE SECOND EFFICACY FOLLOW-UP PERIOD) (TOTAL EFFICACY COHORT) 99
SUPPLEMENT 41: PERCENTAGE OF SUBJECTS REPORTING ANY GE FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD AND EFFICACY OF THE VACCINE (TOTAL EFFICACY COHORT) 100
SUPPLEMENT 42: PERCENTAGE OF SUBJECTS REPORTING SEVERE GE FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD AND EFFICACY OF THE VACCINE (TOTAL EFFICACY COHORT) 101
SUPPLEMENT 43: PERCENTAGE OF SUBJECTS IN THE HRV VACCINE GROUP REPORTING RV GE FROM 2 WEEKS AFTER DOSE 2 UP TO THE END OF THE SECOND EFFICACY FOLLOW-UP PERIOD, BY STATUS OF ANTI-ROTAVIRUS IGA ANTIBODY CONCENTRATION AT VISIT 3 (TOTAL EFFICACY COHORT) 102
SUPPLEMENT 44: DISTRIBUTION OF ANTI-ROTAVIRUS IGA ANTIBODY CONCENTRATIONS (TOTAL IMMUNOGENICITY COHORT) 103

SUPPLEMENT 45: REVERSE CUMULATIVE DISTRIBUTION CURVE FOR ANTI-ROTAVIRUS IGA ANTIBODY CONCENTRATIONS AT VISIT 5 AT THE END OF THE SECOND RV SEASON (TOTAL IMMUNOGENICITY COHORT) 104
SUPPLEMENT 46: ANTI-ROTAVIRUS IGA ANTIBODY GMCS AND SEROPOSITIVITY RATES FOR SUBJECTS WITH RESULTS AVAILABLE AT ALL BLOOD SAMPLING TIMEPOINTS (TOTAL IUNOGENICITY COHORT) 105
SUPPLEMENT 47: DISTRIBUTION OF ANTI-ROTAVIRUS IGA ANTIBODY CONCENTRATIONS FOR SUBJECTS WITH RESULTS AVAILABLE AT ALL BLOOD SAMPLING TIMEPOINTS (TOTAL IMMUNOGENICITY COHORT) 106
SUPPLEMENT 48: ANTI-ROTAVIRUS IGA ANTIBODY GMCS CALCULATED ON SUBJECTS SEROPOSITIVE FOR ANTI-ROTAVIRUS IGA ANTIBODIES FOR SUBJECTS WITH RESULTS AVAILABLE AT ALL BLOOD SAMPLING TIMEPOINTS (TOTAL IMMUNOGENICITY COHORT) 107

APPENDICES

APPENDIX A: CLINTRIAL ELIGIBILITY CODES 108
APPENDIX B: NOTES TO APPENDICES 111
APPENDIX C: MATHEMATICAL DETAILS* ABOUT THE COMPUTATION OF THE 95% CI FOR VACCINE EFFICACY 114

APPENDICES: INDIVIDUAL LISTINGS

Demography

I A ELIMINATION CODES
B DEMOGRAPHY
C DATES OF BIRTH, VACCINATION AND BLOOD SAMPLING
D GENERAL MEDICAL HISTORY - PHYSICAL EXAMINATION
E STUDY CONCLUSION

Reactogenicity

II B SOLICITED GENERAL ADVERSE EVENTS
Ci UNSOLICITED ADVERSE EVENTS WITHIN 43 DAYS POST VACCINATION
Cii UNSOLICITED ADVERSE EVENTS STARTED MORE THAN 43 DAYS POST VACCINATION
Di CONCOMITANT MEDICATION
Dii CONCOMITANT VACCINATION

Immunogenicity

III A IMMUNOGENICITY: IgA ANTIBODY TITERS

Stool analysis

IV A GASTROENTERITIS STOOL COLLECTION RESULTS

Efficacy

V A DETAILED INFORMATION OF GASTROENTERITIS EPISODES

APPENDICES: SERIOUS ADVERSE EVENTS

CLINICAL NARRATIVES FROM OCEANS
SERIOUS ADVERSE EVENTS TABLE

List of Abbreviations

ATP	According to Protocol
CI	Confidence Interval
CRF	Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
ES	End of season
ffu	Foci forming units
GE	Gastroenteritis
GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline
HRV	Human Rotavirus
HIV	Human Immunodeficiency Virus
LL	Lower limit
ml	Milliliter
RAP	Report Analysis Plan
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
U	Units
USA	United States of America
UL	Upper limit

Glossary of Terms

According to protocol cohort:	Includes all subjects enrolled in the study who met the criteria defined in the protocol for the considered analysis (efficacy, reactogenicity or immunogenicity).
Adverse event:	Any noxious, pathologic or unintended change in anatomical, physiologic and/or laboratory detected changes occurring in any phase of the clinical trial whether associated with vaccination or whether or not considered vaccine related.
Asymptomatic rotavirus infections:	Seroconversion (for subjects negative for anti-rotavirus IgA antibody concentration at Visit 3) or ≥ 4-fold increase in IgA antibody concentrations (for subjects positive for anti-rotavirus IgA antibody concentration at Visit 3) between one month after dose 2 (Visit 3) and each end of season sampling time points in subjects who did not report a rotavirus GE episode between one month after Dose 2 and each end of season sampling time points.
Case report form:	Hard copy standardized form for recording individual subject data.
Completed:	Subject who completed the final study visit.
Diarrhea:	Three or more looser than normal stools within a day.
Diary card:	Individual card provided by the sponsor for each vaccinee after each vaccine dose designed to document the presence of solicited adverse events as well as any other sign/symptom the vaccinee might experience.
Drop-out:	Subject who did not return for the final study visit.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.

Enrolled:	Participated in the first visit of the study after written informed consent obtained from parents/guardians, determined to be eligible for inclusion in the study based upon strict adherence to inclusion/exclusion criteria and received vaccination.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in analysis.
Gastroenteritis:	Diarrhea and/or vomiting.
Medical monitor	An individual medically qualified to assure the responsibilities of the sponsor especially as regards the ethics, clinical safety of a study and the assessment of adverse events.
Rotavirus disease seasons	The first season was from December 1, 2000 to June 1, 2001 and the second season was from December 1, 2001 to June 1, 2002.
Rotavirus gastroenteritis for efficacy analysis:	An episode of gastroenteritis occurring at least two weeks after Dose 2 in which rotavirus was identified by ELISA (RT-PCR) in a stool sample collected during an episode of gastroenteritis. Stool samples collected from the start of the gastroenteritis episode to the minimum of the following 2 timepoints either 7 days after the end of the gastroenteritis episode or the day before the next gastroenteritis episode, if subject had several episodes of gastroenteritis were taken into account.
Separate episodes of gastroenteritis:	Two occurrences of gastrointestinal symptoms with 5 or more symptoms-free days between the episodes.
Seroconversion:	Appearance of anti-rotavirus IgA antibody concentration ≥ 20 U/ml in subjects initially (i.e. prior to the first dose) negative for rotavirus.

Seronegative:	A subject whose antibody concentration was below the assay cut-off value.
Seropositive:	A subject whose antibody concentration was greater than or equal to the assay cut-off value.
Severe rotavirus gastroenteritis:	An episode of rotavirus gastroenteritis with score ≥ 11 on a 20 point scoring system.
Site monitor	An individual assigned by GlaxoSmithKline who was responsible for assuring proper conduct of a clinical study at one or more investigational sites.
Study monitor	An individual assigned by and centrally located at GlaxoSmithKline who was responsible for assuring proper conduct of a clinical study.
Subject(s)/Vaccinee(s):	Terms used throughout the report to denote the enrolled/vaccinated individual(s).
Total cohort:	All enrolled subjects for whom data were available.
Vomiting:	One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

1 Introduction/Rationale

Study rota-004 was undertaken to assess the efficacy, reactogenicity, safety and immunogenicity of GSK Biologicals' human rotavirus (HRV) vaccine in the target age group - infants approximately 2 months of age who were previously uninfected with HRV.

Final analysis was performed at the end of the first RV season post-vaccination and the efficacy, reactogenicity, safety and immunogenicity results obtained until the end of the first rotavirus (RV) season following vaccination are presented in the final study report dated April 30, 2003. The final analysis demonstrated the efficacy against RV gastroenteritis (GE) of two doses of GSK Biologicals' HRV vaccine containing strain RIX4414 at a virus concentration of $10^{4.7}$ ffu in infants (6 – 12 weeks old at study entry) previously uninfected with HRV. GSK Biologicals' HRV vaccine was safe and did not appear to be more reactogenic than the placebo. The HRV vaccine was also immunogenic in terms of serum anti-rotavirus IgA antibody response.

Study subjects were followed over the second RV season post-vaccination to evaluate the efficacy of GSK Biologicals' HRV vaccine over two consecutive RV seasons.

This annex report presents analysis of data from the end of the first RV season post-vaccination until the end of the study at the end of the second RV season post-vaccination, as well as efficacy analyses over two consecutive RV seasons.

In the final and the annex analysis, there were either missing results or inconsistencies between the ELISA and RT-PCR test results for GE stool analysis for six subjects. ELISA and/or RT-PCR tests were repeated for these subjects and results of the efficacy reanalysis with the corrected test results are presented in the Erratum dated November 13, 2003.

The data from study 004 is thus presented in three parts:

- Final Study Report dated April 30, 2003
- Annex Report dated November 13, 2003
- Erratum dated November 13, 2003

2 Study Objectives

Note: All study objectives can be found in the final study report dated April 30, 2003. Only objectives pertaining to the annex analysis of this study are mentioned below. Actual viral concentration contained in GSK Biologicals' HRV vaccine is mentioned.

2.1 Secondary objectives

Efficacy

- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent severe RV GE during the period starting from the end of the first RV season following vaccination until the end of the second RV season following vaccination.

- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent any and severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.

- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent any and severe GE of any etiology (RV or not) during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.

- To assess if two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine can prevent asymptomatic RV infections occurring during the period starting from one month after Dose 2 until the end of the second RV season following vaccination.

- To assess if the RV detection method (ELISA *versus* RT-PCR) modifies vaccine efficacy.

- To characterize the G type of the wild RV strain by RT-PCR.

Safety

- To assess the safety of two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine *versus* placebo.

Immunogenicity

- To assess the immunogenicity (serum IgA antibody levels) of two doses of $10^{4.7}$ ffu of GSK Biologicals' HRV vaccine.

See Section 3.14.1 for delineation of secondary endpoints.

3 Methodology

3.1 Study design

Refer to the final study report dated April 30, 2003.

3.2 Investigators and trial centers

Refer to the final study report dated April 30, 2003.

3.3 Ethics

Refer to the final study report dated April 30, 2003.

3.3.1 Protocol amendments/modifications

Refer to the final study report dated April 30, 2003.

3.4 Selection of study population

Refer to the final study report dated April 30, 2003.

3.5 Study vaccines and administration

Refer to the final study report dated April 30, 2003.

3.6 Treatment allocation and randomization

Refer to the final study report dated April 30, 2003.

3.7 Blinding

The study was conducted in a double-blind manner so that parents/guardians of the subjects and the study personnel were unaware of the administered treatment. Dissemination of the treatment code after analysis at the end of the first RV season was controlled until study end. Only summary results were provided in the final study report dated April 30, 2003 and individual subjects' numbers were not specified. Dissemination of the final study report was controlled until study end. Also, refer to the final study report dated April 30, 2003.

3.8 Study procedures

Refer to the final study report dated April 30, 2003 for a summary of all study procedures.

During the RV season, a study nurse contacted the parents/guardians by telephone approximately every two weeks to check on the subject's health and the occurrence of any GE symptoms.

The parents/guardians were instructed to contact the study nurse/investigator by telephone whenever they suspected that the subject had GE from Visit 4 onwards up to Visit 5 and notify the study personnel of the symptoms.

At Visit 5 at the end of the second RV season post-vaccination, the investigator or his/her designee performed a physical examination, checked appropriate elimination criteria and recorded any GE and serious adverse events (SAEs) since the previous visit. Minimum of 1 ml of whole blood was collected from all subjects. Diary cards and any stool samples collected during GE episodes were collected.

3.9 Subject completion and drop-out

A subject who did not return at Visit 5 was considered as a drop-out. A subject who returned for the concluding visit foreseen in the protocol was considered to have completed the study.

Also, refer to the final study report dated April 30, 2003.

3.10 Assessment of efficacy variables

The second efficacy follow-up period started on June 2, 2001 and ended at the end of the second RV season on June 1, 2002. Follow-up visit at the end of the second RV season (Visit 5) occurred between May 21, 2002 and June 26, 2002.

Efficacy during the second efficacy follow-up period after vaccination was assessed using GE follow-up diary cards provided to the parents/guardians of the subjects at Visit 4 to record specific symptoms during any suspected GE episodes occurring until the end of the second RV season after vaccination. GE was defined as diarrhea and/or vomiting.

The RV season in Finland is expected from December 1 to June 1 of each year.

Please refer to the final study report dated April 30, 2003 for information on follow-up of any suspected GE episodes including procedures for completion of GE diary cards, collection of stool samples and assessment of severity.

Serum concentration of RV specific IgA antibodies were measured by ELISA at the end of the second RV season (at Visit 5 which occurred between 21 May, 2002 and June 26, 2002) to detect asymptomatic RV infection. Seroconversion (appearance of anti-rotavirus IgA antibody concentration ≥ 20 U/ml in subjects negative for RV prior to the first dose) or ≥ 4-fold rises of anti-rotavirus antibody IgA concentration between one month post Dose 2 and end of the season time point was considered as a serological evidence of an asymptomatic RV infection.

3.10.1 Laboratory assays and timepoints

Stool sampling

All stool samples collected during any episodes of diarrhea and/or vomiting during the second efficacy follow-up period after vaccination were analyzed by Enzyme Linked Immunosorbent Assay (ELISA) at the Laboratory of Dr. [redacted] Children's Hospital Medical Center, Cincinnati, USA ([1]) and by RT-PCR at the Laboratory of Prof. [redacted] Finland ([2], [3]) to detect the presence of RV. If RV was detected in the stool specimens, the specimens were to be analyzed by RT-PCR to determine the G type at the Laboratory of Prof. [redacted] Finland.

3.11 Assessment of safety variables

The parents/guardians were instructed to contact the investigator immediately if the subject manifested any signs or symptoms during the study that they perceived as serious.

SAEs occurring during the second efficacy follow-up period after vaccination were recorded and followed-up. Please refer to the final study report dated April 30, 2003 for information on definition and follow-up of SAEs.

3.11.1 Pregnancy

Not applicable.

3.11.2 Prior and concomitant medication

Medications administered during the period from end of the first RV season until study end were not recorded.

3.12 Assessment of immunogenicity variables

3.12.1 Laboratory assays and timepoints

Whole blood samples (1 ml) were obtained at Visit 5 from all subjects. Blood samples were centrifuged and separated and all serum samples were stored at –20°C.

Serum anti-rotavirus IgA antibodies were measured by ELISA ([4]) at the Laboratory of Dr. [redacted] Children's Hospital Medical Center, Cincinnati, USA and expressed in units per milliliter (U/ml). The assay cut-off was 20 U/ml

Refer to the final study report dated April 30, 2003 for further details on the laboratory assays.

A seronegative subject for anti-rotavirus IgA antibodies was defined as a subject who had antibody concentration below the assay cut-off value. A seropositive subject for anti-rotavirus IgA antibodies was defined as a subject who had antibody concentration greater than or equal to the assay cut-off value.

3.13 Data quality assurance

Refer to the final study report dated April 30, 2003.

Adherence to the protocol requirements and verification of data generation accuracy was achieved through monitoring visits to each investigator site. Computer checks and blinded review of subject tabulations were performed to ensure consistency of case report form (CRF) completion. All procedures were performed according to methodologies detailed in GSK Biologicals' Standard Operating Procedures.

3.14 Statistical methods

The analyses were performed using Statistical Analysis System (SAS) 8.2 and Proc StatXact-3 on Windows NT 4.0.

Note: All study endpoints can be found in the final study report dated April 30, 2003. Only endpoints pertaining to the annex analysis of this study are mentioned below.

3.14.1 Secondary endpoints

Efficacy endpoints

• Occurrence of severe RV GE during the period starting from the end of the first RV season until the end of the second RV season following vaccination as detected by ELISA and as detected by RT-PCR in stool samples.

• Occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination as detected by ELISA and as detected by RT-PCR in stool samples.

• Occurrence of any and severe GE of any etiology (RV or not) during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.

• Occurrence of asymptomatic RV infections during the period starting from 1 month after Dose 2 until the end of the second RV season following vaccination.

• G type of the wild RV strain by RT-PCR.

Safety endpoints

• Occurrence of serious adverse events after Visit 4 until Visit 5.

Immunogenicity endpoints

• Anti-rotavirus IgA antibody concentrations before Dose 1, one month after Dose 2 and at the end of each RV season.

3.14.2 Determination of sample size

Refer to the final study report dated April 30, 2003.

3.14.3 Study cohorts/data sets analyzed

The following subject cohorts were evaluated during the annex analysis:

Total cohort
The total cohort included all subjects enrolled in the study for whom data were available:

- Efficacy analysis based on the total efficacy cohort included all enrolled subjects for whom efficacy follow-up data were available. Efficacy follow-up was derived from any contact beyond the end of the first efficacy follow-up period for the second efficacy follow-up period and beyond 2 weeks after the second dose of HRV vaccine or placebo for combined efficacy follow-up periods.
- Safety analysis based on the total safety cohort included all enrolled subjects for whom safety data were available.
- Immunogenicity (anti-rotavirus antibody level) analysis based on the total immunogenicity cohort included all enrolled subjects for whom immunogenicity data were available.

ATP efficacy cohort for the second efficacy follow-up period
The ATP efficacy cohort for the second efficacy follow-up period included all subjects from the ATP efficacy cohort of the first efficacy follow-up period:

- who had entered into the surveillance period: had follow-up beyond the end of the first efficacy follow-up period.

Subjects reporting a RV GE episode during the first efficacy follow-up period were **not** eliminated from the ATP efficacy cohort for the second efficacy follow-up period.

ATP efficacy cohort for two consecutive efficacy follow-up periods
The ATP efficacy cohort for combined efficacy follow-up periods includes all subjects from the ATP efficacy cohort of the first efficacy follow-up period.

Refer to the final study report dated April 30, 2003 for the definition of the ATP efficacy cohort for the first efficacy follow-up period.

The respective total cohorts were used for the primary analysis of safety and immunogenicity during the second efficacy follow-up period.

The respective ATP efficacy cohorts were used for the primary analysis of efficacy. Analyses of efficacy on the respective total efficacy cohorts were also performed.

Subjects excluded from the ATP cohorts for the second efficacy follow-up period were identified before data analysis after a review of the individual subject data blinded to group allocation.

Only statistical analyses pertaining to the annex analysis are described below.

3.14.4 Analysis of demographics

Refer to the final study report dated April 30, 2003.

3.14.5 Analysis of efficacy

The second efficacy follow-up period started from June 2, 2001 and ended at the end of the second RV season on June 1, 2002.

The efficacy on combined efficacy follow-up periods started from 2 weeks after Dose 2 and ended at the end of the second RV season on June 1, 2002.

Please refer to the glossary of terms for definition of an episode of RV GE.

A global overview of the number of GE episodes of any etiology (RV or not) and RV GE episodes reported by the subjects during the second efficacy follow-up period and the combined efficacy follow-up periods was provided for each group. The severity of all GE and all RV GE episodes reported during the second efficacy follow-up period and the combined efficacy follow-up periods was tabulated by group. A summary of RV GE episodes reported during the second efficacy follow-up period and the combined efficacy follow-up periods by type was provided.

The percentage of subjects reporting RV GE (any and severe intensity) during the second efficacy follow-up period and the combined efficacy follow-up periods was calculated by group with its 95% Confidence Interval (CI). Two-sided Fisher's exact test (significance level of $\alpha = 0.05$) was used to compare these percentages between groups.

The percentage of subjects hospitalized for GE of any etiology (RV or not) during the second efficacy follow-up period and the combined efficacy follow-up periods was calculated by group with its 95% CI. Two-sided Fisher's exact test (significance level of $\alpha = 0.05$) was used to compare these percentages between groups.

Please refer to the glossary of terms for definition of an episode of asymptomatic RV infection. The percentage of subjects with asymptomatic RV infections between one month after Dose 2 and end of the second RV season following vaccination was calculated by group with its 95% CI. Two-sided Fisher's exact test (significance level of $\alpha = 0.05$) was used to compare these percentages between groups.

The percentage of subjects reporting GE of any etiology (RV or not) (any and severe intensity) during the combined efficacy follow-up periods was calculated by group with its 95% Confidence Interval (CI). Two-sided Fisher's exact test (significance level of $\alpha = 0.05$) was used to compare these percentages between groups.

The efficacy rate (overall and by RV type) of the HRV vaccine relative to the placebo was calculated with its 95% CI against RV GE (any and severe intensity) occurring during the second efficacy follow-up period and the combined efficacy follow-up periods. The efficacy rate with its 95% CI was also calculated against hospitalization due to GE of any etiology (RV or not) occurring during the second efficacy follow-up period and the combined efficacy follow-up periods.

The efficacy rate with its 95% CI was calculated against asymptomatic RV infections occurring between one month after Dose 2 and end of the second RV season following vaccination.

The efficacy rate with its 95% CI was calculated against GE of any etiology (RV or not) (any and severe intensity) occurring during the combined efficacy follow-up periods.

Vaccine efficacy was defined as the percent reduction in the frequency of the considered endpoint in vaccinated subjects compared with those subjects who received placebo.

The vaccine efficacy was calculated using the formula: $1 - RR = 1 - (ARV/ARU)$

RR = relative risk = ARV/ARU

- ARU = disease attack rate in unvaccinated population (estimated from the placebo group) = nu/Nu = number of subjects reporting at least one RV GE episode / total number of subjects in the control group.
- ARV = disease attack rate in vaccinated group = nv/Nv = number of subjects reporting at least one RV GE episode / total number of subjects in the HRV vaccine group.

The 95% CIs for vaccine efficacy were derived using a conditional to cases approach (refer to *Appendix C: Mathematical details about the computation of the 95% CI for vaccine efficacy*).

Also, the person-year rates of RV GE (any and severe intensity), of hospitalization due to any GE and of GE (any and severe intensity) within each group were assessed using a loglinear Poisson model.

The percentages of subjects reporting at least one RV GE episode during the second efficacy follow-up period and the combined efficacy follow-up periods according to serological status for IgA antibodies at one month after Dose 2 were computed.

3.14.6 Analysis of safety

The number of subjects reporting at least one SAE after Visit 4 until Visit 5 was presented per group.

3.14.7 Analysis of immunogenicity

GMCs (Geometric Mean Concentrations) and seropositivity rates to anti-rotavirus IgA antibodies were calculated with their 95% CI for each group, at Visit 5 and tabulated with results from other blood sampling timepoints. GMCs (expressed in U/ml) were computed by giving an arbitrary value of half the cut-off for non-detectable concentrations. Distribution of IgA antibody concentrations at Visit 5 was calculated and tabulated with results from other blood sampling timepoints.

A subject who had seroconverted for anti-rotavirus IgA antibodies at a post-vaccination sampling timepoint either due to vaccine administration or natural HRV infection was defined as a subject with appearance of anti-rotavirus IgA antibody concentration ≥ 20 U/ml in subjects initially (i.e. prior to the first dose) negative for RV. The seroconversion rate was the seropositivity rate at the post-vaccination sampling timepoint in subjects initially negative for RV.

The distribution of IgA antibody concentrations at Visit 5 was displayed using reverse cumulative curves.

At each blood sampling timepoints, anti-rotavirus IgA antibody GMCs were calculated on subjects seropositive for anti-rotavirus IgA antibodies.

Anti-rotavirus IgA antibody GMCs, seropositivity rates and distribution of anti-rotavirus IgA antibody concentrations were calculated for subjects with anti-rotavirus antibody results available at each blood sampling timepoints.

At each blood sampling timepoints and for subjects with anti-rotavirus antibody results available at all blood sample timepoints, anti-rotavirus IgA antibody GMCs were also calculated on subjects seropositive for anti-rotavirus IgA antibodies.

3.15 Interim analysis

Refer to the final study report dated April 30, 2003.

3.16 Annex analysis

Analysis of data from the end of the first year RV season post-vaccination until the end of the study (Visit 5) and efficacy analyses over both efficacy follow-up periods are presented in this annex report.

3.17 Changes in conduct of the study/planned analyses

The following changes were made to the planned annex analyses:

- Vaccine efficacy against hospitalization due to GE of any etiology (RV or not) during the second efficacy follow-up period and the combined efficacy follow-up periods were calculated in accordance with the RAP for the HRV vaccine project to standardize the data with future studies.
- The 95% CIs for vaccine efficacy were derived according to the method described in the RAP for the HRV vaccine project and is presented in Appendix B, rather than using the Mantel-Haenszel approach as specified in the study protocol.
- GMCs to anti-rotavirus IgA antibody on seropositive subjects were calculated to allow comparison to GMCs obtained in other studies.

- [redacted]

  [redacted]

  The rule followed for the repeat tests was as follows: when the repeat test confirmed the results of the first test, the result was considered as the final result. When the repeat test did not confirm the results of the first test, a second repeat was done and the correct result was the result obtained twice.

  Calculations pertaining to the main objectives of the study, i.e. vaccine efficacy, were redone with the corrected ELISA and RT-PCR results. The results of the reanalysis are presented in Erratum dated November 13, 2003. Although the efficacy estimates were slightly higher after the reanalysis, the changes did not alter the study conclusions. The corrected results were also included in a manuscript submitted to the BMJ.

4 Study Population

4.1 Study dates

The study began on August 21, 2000 (first subject, first visit). The data lock point for the final analysis at the end of the first efficacy follow-up period was July 11, 2001 (the day the last Visit 4 was performed). The study ended on June 26, 2002 (the day the last Visit 5 was performed).

4.2 Subject eligibility and attrition from study

4.2.1 Number and distribution of subjects

As planned, 405 subjects were enrolled in the study after checking of inclusion/exclusion criteria. Also, refer to the final study report dated April 30, 2003.

4.2.2 Study completion and drop-out

Thirty-three subjects had dropped out of the study until Visit 4 (refer to the final study report dated April 30, 2003). Nine more subjects failed to return for Visit 5. Thus, a total of 42 subjects did not complete the study for reasons detailed in Table 1.

Table 1: Counts of subjects enrolled, completed Visit 5, dropped out and reason for drop-out (total cohort)

	Group		
	HRV	**Placebo**	**Total**
Number of subjects enrolled	270	135	405
Number of subjects completed	244	119	363
Number of subjects dropped-out	26	16	42
Reasons for drop-out:			
Serious adverse event	0	0	0
Non-serious adverse event	6	2	8
Protocol violation	0	0	0
Consent withdrawal (not due to an adverse event)	14	7	21
Migrated/moved from study area	1	3	4
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0
Lost to follow-up (subjects with complete vaccination course)	5	2	7
Others	0	2	2

Source: Appendix Table IE
Notes: Enrolled = number of subjects who where entered in the study
Completed = number of subjects who completed study Visit 5
Dropped-out = number of subjects who did not return for study Visit 5

[redacted]

Additional information regarding the reason for drop-out became available during the second efficacy follow-up period for three subjects who had not returned for Visit 4. The reason for drop-out at Visit 4, as mentioned in the study report dated April 30, 2003, was therefore changed for three subjects as follows:

[redacted]

4.2.3 Eligibility for analysis

Reasons for elimination from the ATP analyses are summarized in Table 2. See *Appendix A: Clintrial eligibility codes* for definitions of codes.

Refer to the final study report dated April 30, 2003.

Of the 368 subjects included in the ATP efficacy cohort for the first efficacy follow-up period, seven subjects did not enter the second efficacy follow-up period and were eliminated from the ATP efficacy cohort for the second efficacy follow-up period.

Table 2: Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses with reasons for exclusion

	Total	Percent	HRV	Placebo
Number of subjects planned	**405**		**270**	**135**
Number of subjects enrolled (total study cohort)	**405**	**100**	**270**	**135**
Administration of vaccine(s) forbidden in the protocol (code 1040)	4		4	
Randomization failure (code 1050)	3		2	1
Study vaccine dose not administered according to protocol (code 1070)	1		1	
Initially positive or unknown status for RV on the day of Dose 1 (code 1500)	6		4	2
Number of subjects included in the ATP safety cohort	**391**	**96.5**	**259**	**132**
At least one study vaccine dose not administered (code 3010)	22		13	9
Subjects not entered into the first surveillance period (code 3020)	1		1	
Number of subjects included in the ATP efficacy cohort - first efficacy follow-up period and combined efficacy follow-up periods	**368**	**90.9**	**245**	**123**
Subjects not entered into the second surveillance period (code 4020)	7		4	3
Number of subjects included in the ATP efficacy cohort - second efficacy follow-up period	**361**	**89.1**	**241**	**120**

Source: Appendix Table IA
Notes: Percent = percentage of subjects in the considered ATP cohort relative to the total cohort.
Comments: A subject may have more than one elimination code assigned for exclusion to a specific cohort. In that case, the lowest code number is listed in this table.
The ATP cohort for analysis of efficacy during the first efficacy follow-up period and for the combined efficacy follow-up periods includes all enrolled subjects with no elimination codes beginning with one thousand or three thousand; The ATP cohort for analysis of efficacy during the second efficacy follow-up period includes all enrolled subjects with no elimination codes beginning with one thousand, three thousand or code 4020.

The number of subjects in the respective total cohorts (efficacy, immunogenicity and safety) were determined based on the definition of cohorts in Section 3.14.3.

4.2.4 Compliance with protocol specified procedures

A total of 363 of the 405 enrolled subjects completed the study. Therefore compliance with study completion until study end was 89.6%.

For the ATP efficacy cohort, ELISA results for stool samples collected for GE episodes during the second efficacy follow-up period were not available for 7.1% episodes in the HRV vaccine group and 9.9% episodes in the placebo group. RT-PCR analysis results were not available for 4.3% episodes in the HRV vaccine group and 6.6% episodes in the placebo group. Results were unavailable due to stool samples not collected, invalid test results or samples not tested.

Please refer to Section 3.17 for information on reanalysis of GE stool samples for subjects with inconsistent or missing results.

4.3 Demographic characteristics

Refer to the final study report dated April 30, 2003.

5 Analysis of Efficacy

5.1 Analysis of efficacy during the second efficacy follow-up period after vaccination

Analysis of efficacy during the second efficacy follow-up period was performed on the ATP cohort (primary analysis) and the total cohort. See Section 3.14.3 for definition of cohorts identified for analyses and Section 4.2.3 for description of eligibility for analyses.

5.1.1 According to protocol analysis

The ATP efficacy cohort for analysis of efficacy during the second efficacy follow-up period consisted of 361 subjects (241 in the HRV vaccine group and 120 in the placebo group).

5.1.1.1 Characterization of GE episodes reported during the second efficacy follow-up period

The second efficacy follow-up period started on June 2, 2001 and ended at the end of the second RV season on June 1, 2002. The duration of follow-up was similar for the two groups: the mean duration was one year for both groups. Refer to Supplement 1 for duration of follow-up for the second efficacy period.

Table 3 presents a summary of intensity of GE episodes of any etiology (RV or not) and RV GE episodes reported during the second efficacy follow-up period. Supplement 2 presents the number and percentage of subjects who reported GE episodes and RV GE episodes during the second efficacy follow-up period.

As seen from Table 3 and Supplement 2, 119 subjects in the HRV vaccine group reported a total of 184 GE episodes and 58 subjects in the placebo group reported 91 GE episodes during the second efficacy follow-up period.

As seen from Supplement 2, the percentages of subjects who reported GE of any etiology (RV or not) during the second efficacy follow-up period was similar between the two groups (49.4% in the HRV vaccine group and 48.3% in the placebo group). The percentage of subjects reporting RV GE was lower in the HRV vaccine group as compared to the placebo group: 2.9% *versus* 10.0% when ELISA was used for detection of RV and 2.5% *versus* 8.3% when RT-PCR was used for detection of RV.

[redacted] Refer to the Erratum dated November 13, 2003 for results of the reanalysis.

As seen from Table 3, using ELISA, six (50%) episodes of RV GE in the placebo group were noted as severe whereas only two episodes (25%) were noted as severe in the HRV vaccine group.

[redacted] All six severe episodes in the placebo group were attributed to the G1 strain.

Table 3: Number of GE episodes and RV GE episodes reported during the second efficacy follow-up period, by severity (ATP efficacy cohort)

Event	Severity	HRV n	HRV %	Placebo n	Placebo %
Any GE	Mild (1 – 6)	129	70.1	56	61.5
	Moderate (7 – 10)	46	25.0	29	31.9
	Severe (≥ 11)	9	4.9	6	6.6
	Any	184	100	91	100
RV GE by ELISA	Mild (1 – 6)	3	37.5	2	16.7
	Moderate (7 – 10)	3	37.5	4	33.3
	Severe (≥ 11)	2	25.0	6	50.0
	Any	8	100	12	100
RV GE by RT-PCR	Mild (1 – 6)	1	16.7	1	10.0
	Moderate (7 – 10)	3	50.0	3	30.0
	Severe (≥ 11)	2	33.3	6	60.0
	Any	6	100	10	100

Source: Appendix Tables IVA and VA
Notes: n/% = number/percentage of the specified event reported in each group, by severity, among all specified events reported during the second efficacy follow-up period
Any = any specified symptom reported, regardless of severity

Table 4 presents the percentage of subjects reporting RV GE episodes during the second efficacy follow-up period by RV G type. G1 strain was the predominant strain causing RV GE episodes in both groups during the second efficacy follow-up period. In addition to the G1 strain, G9 strain was isolated in one case in the HRV vaccine group.

Table 4: Percentage of subjects with RV GE episodes reported during the second efficacy follow-up period, by RV G type (ATP efficacy cohort)

Type	HRV N = 241 n	HRV N = 241 %	Placebo N = 120 n	Placebo N = 120 %
ELISA				
Any	7	2.9	12	10.0
Unknown	2	0.8	2	1.7
G1	5	2.1	10	8.3
G9	1	0.4	0	0.0
RT-PCR				
Any	6	2.5	10	8.3
G1	5	2.1	10	8.3
G9	1	0.4	0	0.0

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified type in each group
Any = number of subjects reporting at least one RV GE episode, whatever the type

[redacted]
Please refer to Section 3.17 for information on reanalysis of GE stool samples. As a result of the reanalysis, all cases of RV GE could be typed. Refer to the Erratum dated November 13, 2003 for reanalysis with the corrected ELISA and RT-PCR results.

Supplement 3 presents the characteristics of RV GE episodes detected by ELISA. Supplement 4 presents the characteristics of RV GE episodes detected by RT-PCR. One RV GE episode reported in the HRV vaccine group required hospitalization during the second efficacy follow-up period. 1–5% dehydration was noted for one RV GE episode in each group. Oral rehydration was given after one episode of RV GE in the HRV vaccine group and two episodes in the placebo group.

5.1.1.2 Vaccine efficacy against RV GE during the second efficacy follow-up period

Vaccine efficacy as measured by ELISA

Table 5 presents the efficacy of the vaccine against RV GE during the second efficacy follow-up period as measured by ELISA.

The vaccine efficacy against occurrence of RV GE as detected by ELISA during the second efficacy period was 71.0% (95% CI, 20.0–90.3). There was a statistically significant decrease in the percentage of subjects reporting RV GE (detected by ELISA) during the second efficacy follow-up period in the HRV vaccine group as compared to the placebo group ($p = 0.010$, two-sided Fisher's exact test).

The vaccine efficacy against occurrence of severe (score ≥ 11 on intensity scale) RV GE detected by ELISA during the second efficacy follow-up period was 83.4% (95% CI, 7.2–98.4). A statistically significant decrease in the percentage of subjects reporting severe RV GE during the second efficacy follow-up period was detected in the HRV vaccine group as compared to the placebo group ($p = 0.018$, two-sided Fisher's exact test).

Table 5: Percentage of subjects reporting RV GE (any and severe intensity) and efficacy of the vaccine as measured by ELISA during the second efficacy follow-up period (ATP efficacy cohort)

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Any RV GE													
HRV	241	7	236.5	0.030	0.014	0.062	2.9	1.2	5.9	71.0	20.0	90.3	0.010
Placebo	120	12	114.8	0.105	0.059	0.184	10.0	5.3	16.8				
Severe RV GE													
HRV	241	2	237.7	0.008	0.002	0.034	0.8	0.1	3.0	83.4	7.2	98.4	0.018
Placebo	120	6	116.8	0.051	0.023	0.114	5.0	1.9	10.6				

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified intensity in the second efficacy follow-up period, in each group
n/N = percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
n/T = person-year rate of RV GE of the specified intensity in each group
95% CI = 95% confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Vaccine efficacy as measured by RT-PCR

Table 6 presents the efficacy of the vaccine against RV GE during the second efficacy follow-up period as measured by RT-PCR.

The vaccine efficacy against occurrence of RV GE as detected by RT-PCR during the second efficacy period was 70.1% (95% CI, 9.3–91.1). There was a statistically significant decrease in the percentage of subjects reporting RV GE (detected by RT-PCR) during the second efficacy follow-up period in the HRV vaccine group as compared to the placebo group (p = 0.015, two-sided Fisher's exact test).

The vaccine efficacy against occurrence of severe (score ≥ 11 on intensity scale) RV GE detected by RT-PCR during the second efficacy follow-up period was 83.4% (95% CI, 7.2–98.4). A statistically significant decrease in the percentage of subjects reporting severe RV GE during the second efficacy follow-up period was detected in the HRV vaccine group as compared to the placebo group (p = 0.018, two-sided Fisher's exact test).

The use of RT-PCR method for detection of RV did not appear to modify the estimate of vaccine efficacy against any or severe RV GE.

Table 6: Percentage of subjects reporting RV GE (any and severe intensity) and efficacy of the vaccine as measured by RT-PCR during the second efficacy follow-up period (ATP efficacy cohort)

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Any RV GE													
HRV	241	6	237.0	0.025	0.011	0.056	2.5	0.9	5.3	70.1	9.3	91.1	0.015
Placebo	120	10	116.1	0.086	0.046	0.160	8.3	4.1	14.8				
Severe RV GE													
HRV	241	2	237.7	0.008	0.002	0.034	0.8	0.1	3.0	83.4	7.2	98.4	0.018
Placebo	120	6	116.8	0.051	0.023	0.114	5.0	1.9	10.6				

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified intensity in the second efficacy follow-up period, in each group
n/N = percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
n/T = person-year rate of RV GE of the specified intensity in each group
95% CI = 95% confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 5 and Supplement 6 respectively present the efficacy against any and severe RV GE by type. Due to low number of cases attributed to other types (only one case attributed to G9 type), cross-protection data obtained are limited.

5.1.1.3 Vaccine efficacy against hospitalization due to any GE during the second efficacy follow-up period

Supplement 7 presents the efficacy against hospitalization due to GE of any etiology (RV or not) during the second efficacy follow-up period for the ATP efficacy cohort. [redacted] This subject had not seroconverted one month after Dose 2.

5.1.1.4 Occurrence of RV GE in HRV vaccine recipients in relation to serological status for IgA antibody concentration one month after Dose 2

Supplement 8 presents the percentage of subjects reporting at least one RV GE episode during the second efficacy follow-up period by serological status for IgA antibody concentration one month after Dose 2.

As seen in Supplement 8, subjects from the HRV vaccine group who had seroconverted one month after Dose 2 were less likely to develop RV GE. Of the two subjects in the HRV vaccine group who had severe RV GE, one had seroconverted while one had not responded to the vaccine one month after Dose 2.

5.1.2 Analysis of total cohort

The total efficacy cohort for analysis of efficacy during the second efficacy follow-up period consisted of 374 subjects (251 in the HRV vaccine group and 123 in the placebo group).

Efficacy data during the second efficacy follow-up period for the total cohort are presented in Supplement 9 to Supplement 20. No subject with RV GE was eliminated from ATP efficacy cohort. The results of the total cohort analysis were similar to those observed in the ATP cohort.

5.2 Analysis of efficacy over two consecutive efficacy follow-up periods after vaccination

Analysis of efficacy over combined efficacy follow-up periods (two consecutive efficacy follow-up periods) was performed on the ATP cohort (primary analysis) and the total cohort. See Section 3.14.3 for definition of cohorts identified for analyses and Section 4.2.3 for description of eligibility for analyses.

5.2.1 According to protocol analysis

The ATP efficacy cohort for analysis of efficacy over two consecutive efficacy follow-up periods consisted of 368 subjects (245 in the HRV vaccine group and 123 in the placebo group).

5.2.1.1 Characterization of GE episodes reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period

The combined efficacy follow-up period started 2 weeks after Dose 2 and ended at the end of the second RV season on June 1, 2002. The duration of follow-up was similar for the two groups: the mean duration was 1.437 years for the HRV vaccine group and 1.433 years for the placebo group. Refer to Supplement 21 for duration of follow-up for the combined efficacy periods.

Table 7 presents a summary of intensity of any GE episodes and RV GE episodes reported during the combined efficacy follow-up. Supplement 22 presents the number and percentage of subjects who reported GE episodes and RV GE episodes during the combined efficacy follow-up.

As seen from Table 7 and Supplement 22, 162 subjects in the HRV vaccine group reported a total of 296 GE episodes and 80 subjects in the placebo group reported 150 GE episodes during the period starting from 2 weeks after Dose 2 until the end of the second RV season.

As seen from Supplement 22, the percentages of subjects who reported GE of any etiology (RV or not) during this period was similar between the two groups (66.1% in the HRV vaccine group and 65.0% in the placebo group). The percentage of subjects reporting RV GE was lower in the HRV vaccine group as compared to the placebo group: 6.1% *versus* 19.5% when ELISA was used for detection of RV and 6.9% *versus* 17.9% when RT-PCR was used for detection of RV.

As seen from Supplement 22, two subjects had two episodes of RV GE during the period from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period.

- [redacted]
- [redacted]

As seen from Table 7, using ELISA, 11 (44.0%) episodes of RV GE in the placebo group were noted as severe whereas only three episodes (18.8%) were noted as severe in the HRV vaccine group.

[redacted]

Table 7: Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by severity (ATP efficacy cohort)

		HRV		Placebo	
Event	**Severity**	**n**	**%**	**n**	**%**
Any GE	Unknown	2	0.7	0	0.0
	Mild (1-6)	207	69.9	95	63.3
	Moderate (7-10)	73	24.7	41	27.3
	Severe (≥11)	14	4.7	14	9.3
	Any	296	100	150	100
RV GE by ELISA	Mild (1-6)	5	31.3	5	20.0
	Moderate (7-10)	8	50.0	9	36.0
	Severe (≥11)	3	18.8	11	44.0
	Any	16	100	25	100
RV GE by RT-PCR	Mild (1-6)	7	38.9	4	17.4
	Moderate (7-10)	8	44.4	8	34.8
	Severe (≥11)	3	16.7	11	47.8
	Any	18	100	23	100

Source: Appendix Table IVA and VA
Notes: n/% = number/percentage of the specified event reported in each group, by severity, among all specified events reported on combined efficacy follow-up periods
Any = any specified symptom reported, regardless of severity

Table 8 presents the percentage of subjects reporting RV GE episodes from 2 weeks after Dose 2 until the end of the second RV season by RV G type. G1 strain was the predominant strain causing RV GE episodes in both groups during this period. [redacted]

Table 8: Percentage of subjects with RV GE episodes reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by RV G type (ATP efficacy cohort)

Type	HRV N = 245		Placebo N = 123	
	n	%	n	%
ELISA				
Any	15	6.1	24	19.5
Unknown	3	1.2	2	1.6
G1	12	4.9	21	17.1
G2	0	0.0	1	0.8
G9	1	0.4	1	0.8
RT-PCR				
Any	17	6.9	22	17.9
G1	16	6.5	21	17.1
G2	0	0.0	1	0.8
G9	1	0.4	1	0.8

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified type in each group
Any = number of subjects reporting at least one RV GE episode, whatever the type

[redacted] As a result of the reanalysis, all cases of RV GE could be typed. Refer to the Erratum dated November 13, 2003 for reanalysis with the corrected ELISA and RT-PCR results.

Supplement 23 presents the characteristics of RV GE episodes detected by ELISA. Supplement 24 presents the characteristics of RV GE episodes detected by RT-PCR. One RV GE episode reported in the HRV vaccine group required hospitalization during the period starting from 2 weeks after Dose 2 and ending at the end of the second RV season. During this period, 1–5% dehydration was noted for one RV GE episode in the HRV vaccine group and three RV GE episodes in the placebo group. Oral rehydration was given after two episodes of RV GE in the HRV vaccine group and five episodes in the placebo group.

5.2.1.2 Vaccine efficacy against RV GE reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period

Vaccine efficacy as measured by ELISA

Table 9 presents the efficacy of the vaccine against RV GE reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period as measured by ELISA.

The vaccine efficacy against occurrence of RV GE from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period as detected by ELISA was 68.6% (95% CI, 37.7–84.7). There was a statistically significant decrease in the percentage of subjects reporting RV GE (detected by ELISA) over two consecutive rotavirus season after vaccination in the HRV vaccine group as compared to the placebo group ($p < 0.001$, two-sided Fisher's exact test).

The vaccine efficacy against occurrence of severe (score ≥ 11 on intensity scale) RV GE from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period as detected by ELISA was 84.9% (95% CI, 41.5–97.3). A statistically significant decrease in the percentage of subjects reporting severe RV GE over two consecutive rotavirus season after vaccination was detected in the HRV vaccine group as compared to the placebo group ($p = 0.001$, two-sided Fisher's exact test).

Table 9: Percentage of subjects reporting RV GE (any and severe intensity) and efficacy of the vaccine as measured by ELISA from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (ATP efficacy cohort)

Group	N	n	T (year)	n / T rate	n / T 95% CI		n / N %	n / N 95% CI		Vaccine efficacy %	Vaccine efficacy 95% CI		p-value
Any RV GE													
HRV	245	15	340.4	0.044	0.027	0.073	6.1	3.5	9.9	68.6	37.7	84.7	<0.001
Placebo	123	24	157.2	0.153	0.102	0.228	19.5	12.9	27.6				
Severe RV GE													
HRV	245	3	349.8	0.009	0.003	0.027	1.2	0.3	3.5	84.9	41.5	97.3	0.001
Placebo	123	10	168.1	0.059	0.032	0.111	8.1	4.0	14.4				

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified intensity in each group
n/N= percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
n/T= person-year rate of RV GE of the specified intensity in each group
95% CI= 95% confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Vaccine efficacy as measured by RT-PCR

Table 10 presents the efficacy of the vaccine against RV GE reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period as measured by RT-PCR.

The vaccine efficacy against occurrence of RV GE from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period as detected by RT-PCR was 61.2% (95% CI, 23.5–80.7). There was a statistically significant decrease in the percentage of subjects reporting RV GE (detected by RT-PCR) over two consecutive rotavirus season after vaccination in the HRV vaccine group as compared to the placebo group (p = 0.002, two-sided Fisher's exact test).

The vaccine efficacy against occurrence of severe (score ≥ 11 on intensity scale) RV GE from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period detected by RT-PCR was 84.9% (95% CI, 41.5–97.3). A statistically significant decrease in the percentage of subjects reporting severe RV GE over two consecutive rotavirus season after vaccination was detected in the HRV vaccine group as compared to the placebo group (p = 0.001, two-sided Fisher's exact test).

Table 10: Percentage of subjects reporting RV GE (any and severe intensity) and efficacy of the vaccine as measured by RT-PCR from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (ATP efficacy cohort)

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Any RV GE													
HRV	245	17	335.5	0.051	0.031	0.082	6.9	4.1	10.9	61.2	23.5	80.7	0.002
Placebo	123	22	158.6	0.139	0.091	0.211	17.9	11.6	25.8				
Severe RV GE													
HRV	245	3	349.8	0.009	0.003	0.027	1.2	0.3	3.5	84.9	41.5	97.3	0.001
Placebo	123	10	168.1	0.059	0.032	0.111	8.1	4.0	14.4				

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified intensity in each group
n/N = percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
n/T = person-year rate of RV GE of the specified intensity in each group
95% CI = 95% confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

The use of RT-PCR method for detection of RV did not appear to modify the estimate of vaccine efficacy against any or severe RV GE.

Supplement 25 and Supplement 26 respectively present the efficacy against any and severe RV GE by type. Due to low number of cases attributed to other types, cross-protection data obtained are limited.

5.2.1.3 Vaccine efficacy against GE reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period

Table 11 presents the efficacy against any and severe GE reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period.

The proportion of subjects reporting GE of any etiology (RV or not) from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period was similar between the groups: 66.1% in the HRV vaccine group and 65.0% in the placebo group. The percentage of subjects reporting severe GE was lower, although not statistically significant, in the HRV vaccine group as compared to the placebo group and vaccine efficacy of 45% (95% CI, -37.0–77.9) was observed.

Table 11: Percentage of subjects reporting any and severe GE and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (ATP efficacy cohort)

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Any GE													
HRV	245	162	211.4	0.766	0.657	0.894	66.1	59.8	72.0	-1.7	-34.6	22.7	0.907
Placebo	123	80	104.8	0.763	0.613	0.950	65.0	55.9	73.4				
Severe GE													
HRV	245	12	343.5	0.035	0.020	0.062	4.9	2.6	8.4	45.2	-37.0	77.9	0.170
Placebo	123	11	166.3	0.066	0.037	0.119	8.9	4.5	15.4				

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one GE episode of the specified intensity in each group
T = sum of follow-up period expressed in year censored at the first occurrence of GE episode of the specified intensity, in each group
n/N = percentage of subjects reporting at least one GE episode of the specified intensity in each group
n/T = person-year rate of GE of the specified intensity in each group
95% CI = exact 95% confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

5.2.1.4 Efficacy against asymptomatic infection from one month after Dose 2 up to the to the second RV season following vaccination

Table 12 presents the efficacy of the vaccine against asymptomatic RV infection (refer to the glossary for definition) from one month after Dose 2 up to the second RV season time point.

Apart from the subjects with symptomatic RV GE, four subjects in the HRV vaccine group and 10 subjects (using ELISA) in the placebo group (11 subjects in the placebo group using RT-PCR) had serological evidence of an asymptomatic RV infection during the period starting from one month after Dose 2 until the end of the second RV season following vaccination as indicated by seroconversion or ≥ 4-fold rises of anti-RV antibody IgA concentration between one month post Dose 2 and end of the second RV season time point. A statistically significant decrease ($p < 0.05$, two-sided Fisher's exact test) in the percentage of subjects reporting asymptomatic RV infection from one month after Dose 2 until the end of the second RV season following vaccination was observed in the HRV vaccine group as compared to the placebo group. Vaccine efficacy against occurrence of asymptomatic RV infection during the period starting from one month after Dose 2 until the end of the second RV season following vaccination was 82.1% (95% CI, 37.8–95.9) by ELISA and 83.2% (95% CI, 43.4–96.1) by RT-PCR.

Table 12: Percentage of subjects reporting asymptomatic RV infection and efficacy of the vaccine from one month after Dose 2 up to the second RV season time point (ATP efficacy cohort)

						Vaccine efficacy			
Group	**N**	**n**	**%**	**95% CI**		**%**	**95% CI**		**p-value**
ELISA									
HRV	194	4	2.1	0.6	5.2	82.1	37.8	95.9	0.002
Placebo	87	10	11.5	5.7	20.1				
RT-PCR									
HRV	193	4	2.1	0.6	5.2	83.2	43.4	96.1	0.001
Placebo	89	11	12.4	6.3	21.0				

Source: Appendix Tables IIIA, IVA and VA
Notes: N = number of subjects included in each group with available anti-rotavirus IgA antibody concentrations at Visits 3 and 5 and who did not reported a RV GE episode between Visits 3 and 5
n = number of subjects reporting asymptomatic RV infection in each group
% = percentage of subjects reporting asymptomatic RV infection in each group
95% CI = exact 95% confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

5.2.1.5 Vaccine efficacy against hospitalization due to any GE from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period

Supplement 27 presents the efficacy against hospitalization due to GE of any etiology (RV or not). Two subjects from the HRV vaccine group were hospitalized due to GE during the period starting from 2 weeks after Dose 2 and ending at the end of the second efficacy follow-up period.

[redacted]

5.2.1.6 Occurrence of RV GE in HRV vaccine recipients in relation to serological status for IgA antibody concentration one month after Dose 2

Supplement 28 presents the percentage of subjects reporting at least one RV GE episode during the second efficacy follow-up period by serological status for IgA antibody concentration one month after Dose 2.

As seen in Supplement 28, subjects in the HRV vaccine group who had seroconverted one month after Dose 2 were less likely to develop RV GE. Also, out of the three subjects from the HRV vaccine group who had severe RV GE, two had not responded one month after Dose 2.

5.2.2 Analysis of total cohort

The total efficacy cohort for analysis of efficacy during two consecutive efficacy follow-up periods consisted of 381 subjects (255 in the HRV vaccine group and 126 in the placebo group).

Efficacy data for the total cohort are presented in Supplement 29 to Supplement 43. No subject with RV GE was eliminated from ATP efficacy cohort. The results of the total cohort analysis were similar to those observed in the ATP cohort.

6 Analysis of Safety

Refer to the final study report dated April 30, 2003.

6.1 Serious Adverse Events

Appendix: Serious Adverse Events presents a summary table for all SAEs reported during the study (from Visit 1 until Visit 5) and the clinical narratives for all SAEs reported during the study (from Visit 1 until Visit 5).

Nineteen subjects (15 in the HRV vaccine group and 4 in the placebo group) had reported at least one SAE until Visit 4.

After Visit 4 until Visit 5, 20 subjects (13 in the HRV vaccine group and 7 in the placebo group) reported at least one SAE. None of the SAEs were assessed as related to study vaccination. None of the subjects dropped out from the study due to SAEs.

Table 13 presents a summary of SAEs reported after Visit 4 until Visit 5.

Table 13: Subjects with serious adverse events reported after Visit 4 until Visit 5

[redacted]

Comments: *SAE reported by subject n°251 started after the data lock point for the analysis at the end of the first efficacy follow-up period, but was already taken into account in the study report dated April 30, 2003.

Additional information became available for SAEs were stated as “ongoing” at the time of the analysis at the end of the first efficacy follow-up period. Subject number 59 from the HRV vaccine group has recovered while seborrheic rash experienced by subject number 338 from the placebo group was still ongoing at study end.

[redacted] Since the SAE was reported after the data lock point for the analysis at the end of the first efficacy follow-up period, this SAE was not included in the study report dated April 30, 2003. This SAE was still ongoing at study end.

6.2 Non-serious Adverse Events

Non-serious adverse events reported by 18 subjects stated as "ongoing" at the time of the analysis at the end of the first efficacy follow-up period.

[redacted]

Non-serious adverse events reported by 16 subjects were still ongoing at study end and are described below:

[redacted]

Source: Appendix Table IICi and IICii

Additional information became available for non-serious adverse events with outcome "not known" at the time of the analysis at the end of the first efficacy follow-up period. The updated information is given below:

[redacted]

Source: Appendix Table IICi and IICii

7 Analysis of Immunogenicity

7.1 Data sets analyzed

Analysis of anti-rotavirus IgA antibody concentrations at the end of the second efficacy follow-up period was performed only on the total cohort. See Section 3.14.3 for definition of cohorts identified for analyses.

Serum anti-rotavirus IgA antibody results from four subjects were modified after the analysis of the first RV season analysis. Serum samples from four subjects were reanalyzed because there was an error in dilution of samples during the original analysis. The corrected results are given below :

[redacted]

Comment: IR = Invalid result

7.2 Total cohort analysis

The total immunogenicity cohort consisted of 404 subjects (269 in the HRV vaccine group and 135 in the placebo group).

7.2.1 Anti- rotavirus IgA antibody response

Anti-rotavirus IgA antibody GMCs and seropositivity rates at each sampling timepoint are presented in Table 14. Distribution of anti-rotavirus IgA antibody concentrations is presented in Supplement 44. Supplement 45 presents reverse cumulative distribution curves of anti-rotavirus IgA antibody concentrations at the end of the second RV season.

Table 14: Anti-rotavirus IgA antibody GMCs and seropositivity rates by ELISA (total immunogenicity cohort)

Group	Timing	N	≥ 20 U/ml				GMC (U/ml)				
					95% CI			95% CI		Range	
			n	%	L.L.	U.L.	Value	L.L.	U.L.	Min	Max
HRV	Pre	265	0	0.0	0.0	1.4	<20	NA	NA	<20	<20
	PII(M3)	234	187	79.9	74.2	84.9	159.0	127.2	198.7	<20	4161
	ES1	224	170	75.9	69.7	81.3	81.8	67.4	99.1	<20	3211
	ES2	229	154	67.2	60.8	73.3	53.1	43.9	64.4	<20	11749
Placebo	Pre	133	0	0.0	0.0	2.7	<20	NA	NA	<20	<20
	PII(M3)	122	1	0.8	0.0	4.5	<20	NA	NA	<20	668
	ES1	120	22	18.3	11.9	26.4	21.8	16.1	29.5	<20	3014
	ES2	115	33	28.7	20.6	37.9	29.3	21.1	40.7	<20	3422

Source: Appendix Table IIIA
Notes: N = number of subjects with available data
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval
L.L. = lower limit, U.L. = upper limit
Min = Minimum concentration
Max = Maximum concentration
Pre = Pre-vaccination
PII(M3) = one month after the second vaccination
ES1 = end of the first RV season
ES2 = end of the second RV season
Comment: NA = not applicable

The results (Table 14) indicate that in terms of percentage of seropositive subjects and GMCs in the vaccine group, there was a decay in anti-rotavirus IgA antibody levels over time which is expected and generally observed for most of the viral vaccines ([5]). However, the decay in antibody levels had no apparent effect on the observed protective efficacy. Indeed, the vaccine efficacy estimate during the second year of follow-up was similar to that during the first year of follow-up.

In order to compare antibody concentrations induced by the vaccine across studies and also to compare with antibody concentrations induced by the natural RV infection, anti-rotavirus IgA GMCs were calculated on the subjects who had seroconverted after vaccination or natural infection and are presented in Table 15.

As seen from Table 15, at each time point anti-rotavirus IgA antibody levels induced by wild type RV in the placebo group are higher than antibody levels induced by the HRV vaccine.

Table 15: Anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies (total immunogenicity cohort)

Group	Timing	N	GMC (U/ml)				
				95% CI		Range	
			Value	L.L.	U.L.	Min	Max
HRV	PII(M3)	187	318.7	269.8	376.4	28	4161
	ES1	170	159.3	137.4	184.8	24	3211
	ES2	154	119.8	100.6	142.7	27	11749
Placebo	PII(M3)	1	668.0	NA	NA	668	668
	ES1	22	697.3	510.9	951.5	116	3014
	ES2	33	422.2	296.3	601.6	62	3422

Source: Appendix Table IIIA
Notes: N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% confidence interval
Min = Minimum concentration, Max = Maximum concentration
L.L. = lower limit, U.L. = upper limit
PII(M3) = one month after the second vaccination
ES1 = end of the first RV season
ES2 = end of the second RV season
Comment: NA = not applicable

Supplement 46 presents anti-rotavirus IgA antibody GMCs and seropositivity rates for subjects with results available at all blood sampling timepoints and Supplement 47 presents distribution of anti-rotavirus IgA antibody concentrations for subjects with results available at all blood sampling timepoints. Supplement 48 presents anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies for subjects with results available at all blood sampling timepoints.

Although no correlate of protection against RV infection and disease has yet been identified, it is considered that anti-rotavirus IgA antibodies are a strong marker of protection ([6], [7]). Indeed, it was observed that subjects in the HRV vaccine group who had seroconverted at one month post Dose 2 of vaccine, were less likely to develop RV GE over both follow-up periods combined (Supplement 8, Supplement 20, Supplement 28 and Supplement 43).

8 Discussion

This annex analysis provides data on the efficacy during the second RV season and over two consecutive RV seasons after two doses of GSK Biologicals' HRV vaccine containing the strain RIX4414 at a virus concentration of $10^{4.7}$ ffu in infants (6 – 12 weeks old at study entry) previously uninfected with HRV.

GSK Biologicals' HRV vaccine was efficacious in protecting susceptible children against RV GE over two RV epidemic seasons after vaccination. Overall, vaccine efficacy estimates for GSK Biologicals' HRV vaccine were similar to those for the 89-12 parent strain. For the second RV season, efficacy rates for RIX4414 and 89-12 were (71.0% [95% CI, 20.0–90.3] *versus* 76% [95% CI, 54–87]) for any RV GE and (83.4% [95% CI, 7.2–98.4] *versus* 84% [95% CI, 57–94]) for severe RV GE by ELISA. For the two follow-up periods combined, efficacy rates for RIX4414 and 89-12 were (68.6% [95% CI, 37.7–84.7] *versus* 76% [95% CI, 54–87]) for any RV GE and (85% [95% CI, 42–97] *versus* 84% [95% CI, 57–94]) for severe RV GE by ELISA ([8]).

It was observed that the immunogenicity or uptake of vaccine as determined by rotavirus IgA antibody response after vaccination is important in that the rate of RV GE was lower in infants who had responded to the vaccine than in those who had not. Only one of the three infants who had a severe RV GE had seroconverted to the vaccine. Other studies have also found a correlation between the level of IgA antibody induced by the natural RV infection and subsequent reinfection and disease ([6], [7]).

This pilot efficacy trial demonstrated the proof of concept with regards to clinical protection with a safe vaccine, namely GSK Biologicals' HRV vaccine. Given its acceptable profile, the efficacy of GSK Biologicals' HRV vaccine could be further optimized by adjusting the viral concentration to be used in further studies.

9 Overall Conclusions

- GSK Biologicals' HRV vaccine was efficacious in decreasing the incidence of any and severe RV GE relative to the placebo during the period starting from the end of the first RV season following vaccination until the end of the second RV season following vaccination.
- GSK Biologicals' HRV vaccine was efficacious in decreasing the incidence of any and severe RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination.
- During the period starting from 2 weeks after Dose 2 until the end of the second RV season following vaccination, GE of any etiology (RV or not) occurred at similar rates in the HRV vaccine and placebo groups. However, the percentage of subjects reporting severe GE of any etiology was lower, although not statistically significant, in the HRV vaccine group as compared to the placebo group.
- GSK Biologicals' HRV vaccine was efficacious in decreasing the incidence of asymptomatic RV infections relative to the placebo during the period starting from one month after Dose 2 until the end of the second RV season following vaccination.
- The G1 type was predominant among the wild type RV circulating during the second RV season following vaccination.
- The method (ELISA *versus* RT-PCR) used for detection of RV did not appear to modify the estimate of vaccine efficacy against any and severe RV GE during the period starting from the end of the first RV season following vaccination until the end of the second RV season following vaccination and during the entire follow-up period (from 2 weeks after Dose 2 until the end of the second RV season following vaccination).
- GSK Biologicals' HRV vaccine was safe and no vaccination-related SAEs were reported after Visit 4 until Visit 5.

10 References.

[1] Bernstein DI, Smith VE, Sherwood JR, Schiff GM, Sander DS, DeFeudis D, Spriggs DR, Ward RL. Safety and immunogenicity of a live attenuated human rotavirus 89-12 vaccine. Vaccine 1998;16:381-7.

[2] Xu L, Harbour D, McCrae MA. The application of polymerase chain reaction to the detection of rotaviruses in faeces. J Virol Method 1990;27:29-38.

[3] Pang X-L, Joensuu J, Hoshino Y, Kapikan AZ, Vesikari T. Rotaviruses detected by reverse transcription polymerase chain reaction in acute gastroenteritis during a trial of rhesus-human reassortant rotavirus tetravalent vaccine: implications of vaccine efficacy analysis. J Clinical Virol 1999;13(1-2):9-16.

[4] Ward RL, Bernstein DI, Shukla R, *et al*. Effects of antibody to Rotavirus on protection of adults challenged with a human Rotavirus. J. Infect. Dis. 1989;159:79-88.

[5] Glass K, Grenfell BT. Antibody dynamics in childhood diseases: waning and boosting of immunity and the impact of vaccination. J Theor. Biol. 2003;221: 121-31.

[6] Ward RL. Mechanisms of protection against rotavirus in humans and mice. J Infect Dis 1996;174 (Suppl 1);S51-8.

[7]Velaquez FR, Matson DO, Guerrero ML, Shults J, Calva JJ, Morrow AL, Glass RI, Pickering LK, Ruiz-Palacios GM. Serum antibody as a marker of protection against natural rotavirus infection and disease. J Infect Dis 2000; 182:1602-9

[8] Bernstein DI, Sack DA, Reisinger K, Rothstein E, Ward RL. Second year follow-up evaluation of live attenuated human rotavirus vaccine 89-12 in healthy infants. J Infect Dis 2002; 186:1487-9.

Supplement 1: Duration (in years) of the follow-up periods for the second efficacy period (ATP efficacy cohort)

Duration (years) of follow-up period	**HRV N=241**	**Placebo N=120**
Total	238.8	119.4
Mean	0.991	0.995
Minimum	0.027	0.512
Q1	1	1
Median	1	1
Q3	1	1
Maximum	1	1

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
Total = sum of follow-up period expressed in year
Q1= 25th percentile Q3=75th percentile

Supplement 2: Number and percentage of subjects who reported GE episodes and RV GE episodes during the second efficacy follow-up period (ATP efficacy cohort)

Event	Total number of episodes reported	HRV N = 241		Placebo N = 120	
		n	%	n	%
GE					
	1	77	32.0	35	29.2
	2	29	12.0	13	10.8
	3	8	3.3	10	8.3
	4	3	1.2	0	0.0
	5	1	0.4	0	0.0
	8	1	0.4	0	0.0
	Any	119	49.4	58	48.3
RV GE					
ELISA	1	6	2.5	12	10.0
	2	1	0.4	0	0.0
	Any	7	2.9	12	10.0
RT-PCR	1	6	2.5	10	8.3
	Any	6	2.5	10	8.3

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified symptom

Supplement 3: Characteristics of RV GE episodes reported during the second efficacy follow-up period, by ELISA (ATP efficacy cohort)

Characteristics	Parameters or categories	HRV N = 241 Value or n	%	Placebo N = 120 Value or n	%
	N'	8	NA	12	NA
Severity score	Mean	8.13	NA	9.75	NA
	SD	4.853	NA	4.159	NA
	Median	10	NA	10.5	NA
	Minimum	2	NA	2	NA
	Maximum	15	NA	16	NA
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	5	62.5	9	75.0
	5	1	12.5	0	0.0
	≥ 6 days	2	25.0	3	25.0
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	1-3	4	50.0	3	25.0
	4-5	0	0.0	3	25.0
	≥ 6	4	50.0	6	50.0
Duration of vomiting	0 day	2	25.0	2	16.7
	1 day	4	50.0	1	8.3
	2 days	2	25.0	3	25.0
	≥ 3 days	0	0.0	6	50.0
Maximum number of episodes of vomiting/24 hours	0	2	25.0	2	16.7
	1	2	25.0	1	8.3
	2-4	4	50.0	4	33.3
	≥ 5	0	0.0	5	41.7
Maximum fever reported/24 hours (measured rectally)	< 37.1°C	3	37.5	3	25.0
	37.1-38.4°C	0	0.0	4	33.3
	38.5-38.9°C	2	25.0	0	0.0
	≥ 39°C	3	37.5	5	41.7
Treatment	none	6	75.0	10	83.3
	Rehydration	1	12.5	2	16.7
	Hospitalization	1	12.5	0	0.0
Dehydration	none	7	87.5	11	91.7
	1-5%	1	12.5	1	8.3
	≥ 6%	0	0.0	0	0.0

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
N' = number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation
Comment: NA = not applicable

Supplement 4: Characteristics of RV GE episodes reported during the second efficacy follow-up period, by RT-PCR (ATP efficacy cohort)

Characteristics	Parameters or categories	HRV N = 241 Value or n	%	Placebo N = 120 Value or n	%
	N'	6	NA	10	NA
Severity score	Mean	10.17	NA	10.80	NA
	SD	3.601	NA	3.521	NA
	Median	10	NA	12	NA
	Minimum	4	NA	4	NA
	Maximum	15	NA	16	NA
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	3	50.0	7	70.0
	5	1	16.7	0	0.0
	≥ 6 days	2	33.3	3	30.0
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	1-3	2	33.3	2	20.0
	4-5	0	0.0	2	20.0
	≥ 6	4	66.7	6	60.0
Duration of vomiting	0 day	0	0.0	1	10.0
	1 day	4	66.7	1	10.0
	2 days	2	33.3	2	20.0
	≥ 3 days	0	0.0	6	60.0
Maximum number of episodes of vomiting/24 hours	0	0	0.0	1	10.0
	1	2	33.3	0	0.0
	2-4	4	66.7	4	40.0
	≥ 5	0	0.0	5	50.0
Maximum fever reported/24 hours (measured rectally)	< 37.1°C	1	16.7	2	20.0
	37.1-38.4°C	0	0.0	3	30.0
	38.5-38.9°C	2	33.3	0	0.0
	≥ 39°C	3	50.0	5	50.0
Treatment	none	4	66.7	8	80.0
	Rehydration	1	16.7	2	20.0
	Hospitalization	1	16.7	0	0.0
Dehydration	none	5	83.3	9	90.0
	1-5%	1	16.7	1	10.0
	≥ 6%	0	0.0	0	0.0

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
N' = number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation
Comment: NA = not applicable

Supplement 5: Percentage of subjects reporting RV GE (any intensity) and efficacy of the vaccine during the second efficacy follow-up period, by type (ATP efficacy cohort)

Type	Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI	
ELISA or RT-PCR													
G1	HRV	241	5	238.0	0.021	0.009	0.050	2.1	0.7	4.8	75.1	20.1	93.3
	Placebo	120	10	116.1	0.086	0.046	0.160	8.3	4.1	14.8			
ELISA or RT-PCR													
G9	HRV	241	1	237.8	0.004	0.001	0.030	0.4	0.0	2.3	infinity	infinity	98.7
	Placebo	120	0	119.4	0.000	NE		0.0	0.0	3.0			

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified type in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified type in the second efficacy follow-up period, in each group
n/N = percentage of subjects reporting at least one RV GE episode of the specified type in each group
n/T = person-year rate of RV GE episode of the specified type in each group
NE = cannot be estimated 95% CI = 95% confidence intervals

Supplement 6: Percentage of subjects reporting severe RV GE and efficacy of the vaccine during the second efficacy follow-up period, by type (ATP efficacy cohort)

Type	Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI	
ELISA or RT-PCR													
G1	HRV	241	1	238.7	0.004	0.001	0.030	0.4	0.0	2.3	91.7	31.6	99.8
	Placebo	120	6	116.8	0.051	0.023	0.114	5.0	1.9	10.6			
ELISA or RT-PCR													
G9	HRV	241	1	237.8	0.004	0.001	0.030	0.4	0.0	2.3	infinity	infinity	98.7
	Placebo	120	0	119.4	0.0	NE		0.0	0.0	3.0			

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode of the specified type in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode of the specified type in the second efficacy follow-up period, in each group
n/N = percentage of subjects reporting at least one severe RV GE episode of the specified type in each group
n/T = person-year rate of severe RV GE episode of the specified type in each group
NE = cannot be estimated 95% CI = 95% confidence intervals

Supplement 7: Percentage of subjects hospitalized due to any GE and efficacy of the vaccine during the second efficacy follow-up period (ATP efficacy cohort)

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
HRV	241	1	237.8	0.004	0.001	0.030	0.4	0.0	2.3	infinity	infinity	98.7	1.000
Placebo	120	0	119.4	0.000	NE		0.0	0.0	3.0				

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects hospitalized due to GE in each group
T = sum of follow-up period expressed in year censored at the first occurrence of hospitalization due to GE in the second efficacy follow-up period, in each group
n/N = percentage of subjects hospitalized due to GE in each group
n/T = person-year rate of hospitalization due to GE in each group
95% CI = 95% confidence intervals
NE = cannot be estimated p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 8: Percentage of subjects in the HRV vaccine group reporting RV GE during the second efficacy follow-up period, by status of anti-rotavirus IgA antibody concentration at Visit 3 (ATP efficacy cohort)

Anti-rotavirus IgA antibody status at Visit 3	**N**	**n**	**%**	**95% CI**	
ELISA					
Negative	45	2	4.4	0.5	15.2
Positive	180	4	2.2	0.6	5.6
Unknown	16	1	6.3	0.2	30.2
RT-PCR					
Negative	45	2	4.4	0.5	15.2
Positive	180	4	2.2	0.6	5.6
Unknown	16	0	0.0	0.0	20.6

Source: Appendix Tables IIIA, IVA and VA

Notes: N = number of subjects included in the vaccine group with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 (Visit 3)
n/% = number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 reporting at least one RV GE episode during the second efficacy follow-up period
95% CI = exact 95% confidence intervals

Supplement 9: Number and percentage of subjects who reported GE episode(s) during the second efficacy follow-up period (total efficacy cohort)

Event	Total number of episodes reported	HRV N = 251		Placebo N = 123	
		n	%	n	%
GE	1	79	31.5	35	28.5
	2	29	11.6	14	11.4
	3	9	3.6	10	8.1
	4	3	1.2	0	0.0
	5	1	0.4	0	0.0
	8	1	0.4	0	0.0
	Any	122	48.6	59	48.0
RV GE					
ELISA	1	6	2.4	12	9.8
	2	1	0.4	0	0.0
	Any	7	2.8	12	9.8
RT-PCR	1	6	2.4	10	8.1
	Any	6	2.4	10	8.1

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified symptom

Supplement 10: Number of any GE episodes and RV GE episodes reported during the second efficacy follow-up period, by severity (total efficacy cohort)

Event	Severity	HRV n	HRV %	Placebo n	Placebo %
GE	Mild (1-6)	131	69.3	58	62.4
	Moderate (7-10)	49	25.9	29	31.2
	Severe (≥11)	9	4.8	6	6.5
	Any	189	100	93	100
RV GE by ELISA	Mild (1-6)	3	37.5	2	16.7
	Moderate (7-10)	3	37.5	4	33.3
	Severe (≥11)	2	25.0	6	50.0
	Any	8	100	12	100
RV GE by RT-PCR	Mild (1-6)	1	16.7	1	10.0
	Moderate (7-10)	3	50.0	3	30.0
	Severe (≥11)	2	33.3	6	60.0
	Any	6	100	10	100

Source: Appendix Tables IVA and VA
Notes: n/% = number/percentage of the specified event reported in each group, by severity, among all specified events reported during the second efficacy follow-up period
Any = any specified symptom reported, regardless of severity

Supplement 11: Percentage of subjects with RV GE episodes reported during the second efficacy follow-up period, by type (total efficacy cohort)

Type	HRV N = 251 n	%	Placebo N = 123 n	%
ELISA				
Any	7	2.8	12	9.8
Unknown	2	0.8	2	1.6
G1	5	2.0	10	8.1
G9	1	0.4	0	0.0
RT-PCR				
Any	6	2.4	10	8.1
G1	5	2.0	10	8.1
G9	1	0.4	0	0.0

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified type in each group
Any = number of subjects reporting at least one RV GE episode, whatever the type

Supplement 12: Characteristics of RV GE episodes reported during the second efficacy follow-up period, by ELISA (total efficacy cohort)

Characteristics	Parameters or categories	HRV N = 251 Value or n	%	Placebo N = 123 Value or n	%
	N'	8	NA	12	NA
Severity score	Mean	8.13	NA	9.75	NA
	SD	4.853	NA	4.159	NA
	Median	10.0	NA	10.5	NA
	Minimum	2	NA	2	NA
	Maximum	15	NA	16	NA
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	5	62.5	9	75.0
	5	1	12.5	0	0.0
	≥ 6 days	2	25.0	3	25.0
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	1-3	4	50.0	3	25.0
	4-5	0	0.0	3	25.0
	≥ 6	4	50.0	6	50.0
Duration of vomiting	0 day	2	25.0	2	16.7
	1 day	4	50.0	1	8.3
	2 days	2	25.0	3	25.0
	≥ 3 days	0	0.0	6	50.0
Maximum number of episodes of vomiting/24 hours	0	2	25.0	2	16.7
	1	2	25.0	1	8.3
	2-4	4	50.0	4	33.3
	≥ 5	0	0.0	5	41.7
Maximum fever reported /24 hours (measured rectally)	< 37.1°C	3	37.5	3	25.0
	37.1-38.4°C	0	0.0	4	33.3
	38.5-38.9°C	2	25.0	0	0.0
	≥ 39°C	3	37.5	5	41.7
Treatment	none	6	75.0	10	83.3
	Rehydration	1	12.5	2	16.7
	Hospitalization	1	12.5	0	0.0
Dehydration	none	7	87.5	11	91.7
	1-5%	1	12.5	1	8.3
	≥ 6%	0	0.0	0	0.0

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
N' = number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter SD= standard deviation
Comment: NA = not applicable

Supplement 13: Characteristics of RV GE episodes reported during the second efficacy follow-up period, by RT-PCR (total efficacy cohort)

Characteristics	Parameters or categories	HRV N = 251 Value or n	%	Placebo N = 123 Value or n	%
	N'	6	NA	10	NA
Severity score	Mean	10.17	NA	10.80	NA
	SD	3.601	NA	3.521	NA
	Median	10.0	NA	12.0	NA
	Minimum	4	NA	4	NA
	Maximum	15	NA	16	NA
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	3	50.0	7	70.0
	5	1	16.7	0	0.0
	≥ 6 days	2	33.3	3	30.0
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	1-3	2	33.3	2	20.0
	4-5	0	0.0	2	20.0
	≥ 6	4	66.7	6	60.0
Duration of vomiting	0 day	0	0.0	1	10.0
	1 day	4	66.7	1	10.0
	2 days	2	33.3	2	20.0
	≥ 3 days	0	0.0	6	60.0
Maximum number of episodes of vomiting/24 hours	0	0	0.0	1	10.0
	1	2	33.3	0	0.0
	2-4	4	66.7	4	40.0
	≥ 5	0	0.0	5	50.0
Maximum fever reported/24 hours (measured rectally)	< 37.1°C	1	16.7	2	20.0
	37.1-38.4°C	0	0.0	3	30.0
	38.5-38.9°C	2	33.3	0	0.0
	≥ 39°C	3	50.0	5	50.0
Treatment	none	4	66.7	8	80.0
	Rehydration	1	16.7	2	20.0
	Hospitalization	1	16.7	0	0.0
Dehydration	none	5	83.3	9	90.0
	1-5%	1	16.7	1	10.0
	≥ 6%	0	0.0	0	0.0

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
N' = number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter SD= standard deviation
Comment: NA = not applicable

Supplement 14: Duration (in years) of the follow-up periods for the second efficacy period (total efficacy cohort)

Duration (years) of follow-up period	**HRV N=251**	**Placebo N=123**
Total	247.9	122.4
Mean	0.987	0.995
Minimum	0.027	0.512
Q1	1	1
Median	1	1
Q3	1	1
Maximum	1	1

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
Total = sum of follow-up period expressed in year
Q1 = 25th percentile Q3 = 75th percentile

Supplement 15: Percentage of subjects reporting RV GE and efficacy of the vaccine as measured by ELISA during the second efficacy follow-up period (total efficacy cohort)

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Any RV GE													
HRV	251	7	245.6	0.029	0.014	0.060	2.8	1.1	5.7	71.4	21.2	90.5	0.010
Placebo	123	12	117.8	0.102	0.058	0.179	9.8	5.1	16.4				
Severe RV GE													
HRV	251	2	246.8	0.008	0.002	0.032	0.8	0.1	2.8	83.7	8.6	98.4	0.017
Placebo	123	6	119.8	0.050	0.022	0.111	4.9	1.8	10.3				

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified intensity in the second efficacy follow-up period, in each group
n/N = percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
n/T = person-year rate of RV GE episode of the specified intensity in each group
95% CI = 95% confidence intervals p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 16: Percentage of subjects reporting severe RV GE and efficacy of the vaccine as measured by RT-PCR during the second efficacy follow-up period (total efficacy cohort)

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Any RV GE													
HRV	251	6	246.1	0.024	0.011	0.054	2.4	0.9	5.1	70.6	10.7	91.2	0.014
Placebo	123	10	119.1	0.084	0.045	0.156	8.1	4.0	14.4				
Severe RV GE													
HRV	251	2	246.8	0.008	0.002	0.032	0.8	0.1	2.8	83.7	8.6	98.4	0.017
Placebo	123	6	119.8	0.050	0.022	0.111	4.9	1.8	10.3				

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode of the specified intensity in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode of the specified intensity in the second efficacy follow-up period, in each group
n/N = percentage of subjects reporting at least one severe RV GE episode of the specified intensity in each group
n/T = person-year rate of severe RV GE episode of the specified intensity in each group
95% CI = 95% confidence intervals p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 17: Percentage of subjects reporting RV GE (any intensity) and efficacy of the vaccine during the second efficacy follow-up period, by type (total efficacy cohort)

Type	Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI	
ELISA or RT-PCR													
G1	HRV	251	5	247.1	0.020	0.008	0.049	2.0	0.6	4.6	75.5	21.3	93.4
	Placebo	123	10	119.1	0.084	0.045	0.156	8.1	4.0	14.4			
ELISA or RT-PCR													
G9	HRV	251	1	246.9	0.004	0.001	0.030	0.4	0.0	2.2	infinity	infinity	98.7
	Placebo	123	0	122.4	0.000	NE		0.0	0.0	3.0			

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified type in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified type in the second efficacy follow-up period, in each group
n/N = percentage of subjects reporting at least one RV GE episode of the specified type in each group
n/T = person-year rate of RV GE episode of the specified type in each group
NE = cannot be estimated 95% CI = 95% confidence intervals

Supplement 18: Percentage of subjects reporting severe RV GE and efficacy of the vaccine during the second efficacy follow-up period, by type (total efficacy cohort)

Serotype	Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI	
ELISA / RT-PCR													
G1	HRV	251	1	247.7	0.004	0.001	0.029	0.4	0.0	2.2	91.8	32.7	99.8
	Placebo	123	6	119.8	0.050	0.022	0.111	4.9	1.8	10.3			
ELISA / RT-PCR													
G9	HRV	251	1	246.9	0.004	0.001	0.030	0.4	0.0	2.2	infinity	infinity	98.7
	Placebo	123	0	122.4	0.000	NE		0.0	0.0	3.0			

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode of the specified type in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode of the specified type in the second efficacy follow-up period, in each group
n/N = percentage of subjects reporting at least one severe RV GE episode of the specified type in each group
n/T = person-year rate of severe RV GE episode of the specified type in each group
NE = cannot be estimated 95% CI = 95% confidence intervals

Supplement 19: Percentage of subjects hospitalized due to any GE and efficacy of the vaccine during the second efficacy follow-up period (total efficacy cohort)

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
HRV	251	1	246.9	0.004	0.001	0.030	0.4	0.0	2.2	infinity	infinity	98.7	1.000
Placebo	123	0	122.4	0.000	NE		0.0	0.0	3.0				

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects hospitalized due to GE in each group
T = sum of follow-up period expressed in year censored at the first occurrence of hospitalization due to GE in the second efficacy follow-up period, in each group
n/N = percentage of subjects hospitalized due to GE in each group
n/T = person-year rate of hospitalization due to GE in each group
95% CI = 95% confidence intervals NE = cannot be estimated
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 20: Percentage of subjects in the HRV group reporting RV GE during the second efficacy follow-up period, by status of anti-rotavirus IgA antibody concentration at Visit 3 (total efficacy cohort)

Anti-rotavirus IgA antibody status at Visit 3	N	n	%	95% CI	
ELISA					
Negative	47	2	4.3	0.5	14.5
Positive	186	4	2.2	0.6	5.4
Unknown	18	1	5.6	0.1	27.3
RT-PCR					
Negative	47	2	4.3	0.5	14.5
Positive	186	4	2.2	0.6	5.4
Unknown	18	0	0.0	0.0	18.5

Source: Appendix Tables IIIA, IVA and VA

Notes: N = number of subjects included in the vaccine group with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 (Visit 3)
n/% = number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 reporting at least one RV GE episode during the second efficacy follow-up period
95% CI = exact 95% confidence intervals

Supplement 21: Duration (in years) of the follow-up periods from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (ATP efficacy cohort)

Duration (years) of follow-up period	**HRV N=245**	**Placebo N=123**
Total	352.1	176.2
Mean	1.437	1.433
Minimum	0.016	0.121
Q1	1.414	1.414
Median	1.468	1.468
Q3	1.510	1.521
Maximum	1.595	1.584

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
Total = sum of follow-up period expressed in year
Q1 = 25th percentile Q3 = 75th percentile

Supplement 22: Number and percentage of subjects who reported GE episodes and RV GE episodes from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (ATP efficacy cohort)

Event	Total number of episodes reported	HRV N = 245		Placebo N = 123	
		n	%	n	%
GE	1	85	34.7	37	30.1
	2	44	18.0	24	19.5
	3	21	8.6	15	12.2
	4	6	2.4	2	1.6
	5	3	1.2	0	0.0
	6	1	0.4	2	1.6
	7	1	0.4	0	0.0
	8	1	0.4	0	0.0
	Any	162	66.1	80	65.0
RV GE by ELISA	1	14	5.7	23	18.7
	2	1	0.4	1	0.8
	Any	15	6.1	24	19.5
RV GE by RT-PCR	1	16	6.5	21	17.1
	2	1	0.4	1	0.8
	Any	17	6.9	22	17.9

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified symptom

Supplement 23: Characteristics of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by ELISA (ATP efficacy cohort)

Characteristics	Parameters or categories	HRV N = 245 Value or n	%	Placebo N = 123 Value or n	%
	N'	16	NA	25	NA
Severity score	Mean	7.94	NA	9.80	NA
	SD	3.568	NA	4.021	NA
	Median	8.5	NA	9.0	NA
	Minimum	2	NA	2	NA
	Maximum	15	NA	17	NA
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	12	75.0	18	72.0
	5	2	12.5	2	8.0
	≥ 6 days	2	12.5	5	20.0
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	1-3	10	62.5	5	20.0
	4-5	0	0.0	7	28.0
	≥ 6	6	37.5	13	52.0
Duration of vomiting	0 day	3	18.8	4	16.0
	1 day	6	37.5	6	24.0
	2 days	6	37.5	5	20.0
	≥ 3 days	1	6.3	10	40.0
Maximum number of episodes of vomiting/24 hours	0	3	18.8	4	16.0
	1	4	25.0	4	16.0
	2-4	8	50.0	8	32.0
	≥ 5	1	6.3	9	36.0
Maximum fever reported/24 hours (measured rectally)	< 37.1°C	3	18.8	3	12.0
	37.1-38.4°C	4	25.0	8	32.0
	38.5-38.9°C	4	25.0	4	16.0
	≥ 39°C	5	31.3	10	40.0
Treatment	none	13	81.3	20	80.0
	Rehydration	2	12.5	5	20.0
	Hospitalization	1	6.3	0	0.0
Dehydration	none	15	93.8	22	88.0
	1-5%	1	6.3	3	12.0
	≥ 6%	0	0.0	0	0.0

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
N' = number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation
Comment: NA = not applicable

Supplement 24: Characteristics of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (ATP efficacy cohort)

Characteristics	Parameters or categories	HRV N = 245 Value or n	%	Placebo N = 123 Value or n	%
	N'	18	NA	23	NA
Severity score	Mean	7.78	NA	10.26	NA
	SD	3.246	NA	3.781	NA
	Median	7.5	NA	10.0	NA
	Minimum	3	NA	4	NA
	Maximum	15	NA	17	NA
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	14	77.8	16	69.6
	5	2	11.1	2	8.7
	≥ 6 days	2	11.1	5	21.7
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	1-3	11	61.1	4	17.4
	4-5	1	5.6	6	26.1
	≥ 6	6	33.3	13	56.5
Duration of vomiting	0 day	4	22.2	3	13.0
	1 day	7	38.9	6	26.1
	2 days	6	33.3	4	17.4
	≥ 3 days	1	5.6	10	43.5
Maximum number of episodes of vomiting/24 hours	0	4	22.2	3	13.0
	1	4	22.2	3	13.0
	2-4	9	50.0	8	34.8
	≥ 5	1	5.6	9	39.1
Maximum fever reported/24 hours (measured rectally)	< 37.1°C	2	11.1	2	8.7
	37.1-38.4°C	5	27.8	7	30.4
	38.5-38.9°C	6	33.3	4	17.4
	≥ 39°C	5	27.8	10	43.5
Treatment	none	15	83.3	18	78.3
	Rehydration	2	11.1	5	21.7
	Hospitalization	1	5.6	0	0.0
Dehydration	none	17	94.4	20	87.0
	1-5%	1	5.6	3	13.0
	≥ 6%	0	0.0	0	0.0

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
N' = number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation
Comment: NA = not applicable

Supplement 25: Percentage of subjects reporting RV GE (any intensity) and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by type (ATP efficacy cohort)

Type	Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI	
ELISA													
G1	HRV	245	12	343.2	0.035	0.020	0.062	4.9	2.6	8.4	71.3	38.9	87.1
	Placebo	123	21	160.6	0.131	0.085	0.201	17.1	10.9	24.9			
RT-PCR													
G1	HRV	245	16	336.5	0.048	0.029	0.078	6.5	3.8	10.4	61.7	23.1	81.3
	Placebo	123	21	160.6	0.131	0.085	0.201	17.1	10.9	24.9			
ELISA / RT-PCR													
G2	HRV	245	0	352.1	0.000	NE		0.0	0.0	1.5	100	-1858	100
	Placebo	123	1	175.0	0.006	0.001	0.040	0.8	0.0	4.4			
ELISA / RT-PCR													
G9	HRV	245	1	351.1	0.003	0.000	0.020	0.4	0.0	2.3	49.8	-3841	99.4
	Placebo	123	1	175.1	0.006	0.001	0.041	0.8	0.0	4.4			

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified type in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified type in each group
n/N = percentage of subjects reporting at least one RV GE episode of the specified type in each group
n/T = person-year rate of RV GE episodes of the specified type in each group
NE = cannot be estimated 95% CI = 95% confidence intervals

Supplement 26: Percentage of subjects reporting severe RV GE and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by type (ATP efficacy cohort)

Type	Group	N	n	T (year)	n / T rate	n / T 95% CI		n / N %	n / N 95% CI		Vaccine efficacy %	Vaccine efficacy 95% CI	
ELISA / RT-PCR													
G1	HRV	245	2	350.8	0.006	0.001	0.023	0.8	0.1	2.9	90.0	52.9	98.9
	Placebo	123	10	169.0	0.059	0.032	0.110	8.1	4.0	14.4			
ELISA / RT-PCR													
G2	HRV	245	0	352.1	0.000	NE		0.0	0.0	1.5	100	-1858	100
	Placebo	123	1	175.0	0.006	0.001	0.040	0.8	0.0	4.4			
ELISA / RT-PCR													
G9	HRV	245	1	351.1	0.003	0.000	0.020	0.4	0.0	2.3	infinity	infinity	98.7
	Placebo	123	0	176.2	0.000	NE		0.0	0.0	3.0			

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode of the specified type in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode of the specified type in each group
n/N = percentage of subjects reporting at least one severe RV GE episode of the specified type in each group
n/T = person-year rate of severe RV GE episode of the specified type in each group
NE = cannot be estimated 95% CI = 95% confidence intervals

Supplement 27: Percentage of subjects hospitalized due to any GE and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (ATP efficacy cohort)

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
HRV	245	2	349.8	0.006	0.001	0.020	0.8	0.1	2.9	infinity	infinity	90.6	0.554
Placebo	123	0	176.2	0.000	NE		0.0	0.0	3.0				

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects hospitalized due to GE in each group
T = sum of follow-up period expressed in year censored at the first occurrence of hospitalization due to GE in each group
n/N = percentage of subjects hospitalized due to GE in each group
n/T = person-year rate of hospitalization due to GE in each group
95% CI = 95% confidence intervals
NE = cannot be estimated p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 28: Percentage of subjects in the HRV vaccine group reporting RV GE from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by status of anti-rotavirus IgA antibody concentration at Visit 3 (ATP efficacy cohort)

Anti-rotavirus IgA antibody status at Visit 3	**N**	**n**	**%**	**95% CI**	
ELISA					
Negative	45	6	13.3	5.1	26.8
Positive	181	7	3.9	1.6	7.8
Unknown	19	2	10.5	1.3	33.1
RT-PCR					
Negative	45	7	15.6	6.5	29.5
Positive	181	9	5.0	2.3	9.2
Unknown	19	1	5.3	0.1	26.0

Source: Appendix Tables IIIA, IVA and VA

Notes: N = number of subjects included in the vaccine group with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 (Visit 3)
n/% = number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 reporting at least one RV GE episode during the second efficacy follow-up period
95% CI = exact 95% confidence intervals

Supplement 29: Number and percentage of subjects who reported GE episode(s) from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (total efficacy cohort)

Event	Total number of episodes reported	HRV N = 255		Placebo N = 126	
		n	%	n	%
GE	1	87	34.1	38	30.2
	2	44	17.3	25	19.8
	3	21	8.2	15	11.9
	4	7	2.7	2	1.6
	5	3	1.2	0	0.0
	6	1	0.4	2	1.6
	7	1	0.4	0	0.0
	8	1	0.4	0	0.0
	Any	165	64.7	82	65.1
RV GE by ELISA	1	14	5.5	23	18.3
	2	1	0.4	1	0.8
	Any	15	5.9	24	19.0
RV GE by RT-PCR	1	16	6.3	21	16.7
	2	1	0.4	1	0.8
	Any	17	6.7	22	17.5

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified symptom

Supplement 30: Number of any GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by severity (total efficacy cohort)

		HRV		Placebo	
Event	**Severity**	**n**	**%**	**n**	**%**
GE	Unknown	2	0.7	0	0.0
	Mild (1-6)	210	69.5	98	64.1
	Moderate (7-10)	76	25.2	41	26.8
	Severe (≥11)	14	4.6	14	9.2
	Any	302	100	153	100
RV GE ELISA	Mild (1-6)	5	31.3	5	20.0
	Moderate (7-10)	8	50.0	9	36.0
	Severe (≥11)	3	18.8	11	44.0
	Any	16	100	25	100
RV GE RT-PCR	Mild (1-6)	7	38.9	4	17.4
	Moderate (7-10)	8	44.4	8	34.8
	Severe (≥11)	3	16.7	11	47.8
	Any	18	100	23	100

Source: Appendix Tables IVA and VA
Notes: n/% = number/percentage of the specified event reported in each group, by severity, among all specified events reported on combined efficacy follow-up periods
Any = any specified symptom reported, regardless of severity

Supplement 31: Percentage of subjects with RV GE episodes reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by type (total efficacy cohort)

	HRV N = 255		Placebo N = 126	
Type	**n**	**%**	**n**	**%**
ELISA				
Any	15	5.9	24	19.0
Unknown	3	1.2	2	1.6
G1	12	4.7	21	16.7
G2	0	0.0	1	0.8
G9	1	0.4	1	0.8
RT-PCR				
Any	17	6.7	22	17.5
G1	16	6.3	21	16.7
G2	0	0.0	1	0.8
G9	1	0.4	1	0.8

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified type in each group
Any = number of subjects reporting at least one RV GE episode, whatever the type

Supplement 32: Characteristics of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by ELISA (total efficacy cohort)

Characteristics	Parameters or categories	HRV N = 255 Value or n	%	Placebo N = 126 Value or n	%
	N'	16	NA	25	NA
Severity score	Mean	7.94	NA	9.80	NA
	SD	3.568	NA	4.021	NA
	Median	8.5	NA	9.0	NA
	Minimum	2	NA	2	NA
	Maximum	15	NA	17	NA
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	12	75.0	18	72.0
	5	2	12.5	2	8.0
	≥ 6 days	2	12.5	5	20.0
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	1-3	10	62.5	5	20.0
	4-5	0	0.0	7	28.0
	≥ 6	6	37.5	13	52.0
Duration of vomiting	0 day	3	18.8	4	16.0
	1 day	6	37.5	6	24.0
	2 days	6	37.5	5	20.0
	≥ 3 days	1	6.3	10	40.0
Maximum number of episodes of vomiting/24 hours	0	3	18.8	4	16.0
	1	4	25.0	4	16.0
	2-4	8	50.0	8	32.0
	≥ 5	1	6.3	9	36.0
Maximum fever reported /24 hours (measured rectally)	< 37.1°C	3	18.8	3	12.0
	37.1-38.4°C	4	25.0	8	32.0
	38.5-38.9°C	4	25.0	4	16.0
	≥ 39°C	5	31.3	10	40.0
Treatment	none	13	81.3	20	80.0
	Rehydration	2	12.5	5	20.0
	Hospitalization	1	6.3	0	0.0
Dehydration	none	15	93.8	22	88.0
	1-5%	1	6.3	3	12.0
	≥ 6%	0	0.0	0	0.0

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
N' = number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter SD= standard deviation
Comment: NA = not applicable

Supplement 33: Characteristics of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by RT-PCR (total efficacy cohort)

Characteristics	Parameters or categories	HRV N = 255 Value or n	%	Placebo N = 126 Value or n	%
	N'	18	NA	23	NA
Severity score	Mean	7.78	NA	10.26	NA
	SD	3.246	NA	3.781	NA
	Median	7.5	NA	10.0	NA
	Minimum	3	NA	4	NA
	Maximum	15	NA	17	NA
Duration of looser than normal stools (days)	0 day	0	0.0	0	0.0
	1-4 days	14	77.8	16	69.6
	5	2	11.1	2	8.7
	≥ 6 days	2	11.1	5	21.7
Maximum number of looser than normal stools/24 hours	0	0	0.0	0	0.0
	1-3	11	61.1	4	17.4
	4-5	1	5.6	6	26.1
	≥ 6	6	33.3	13	56.5
Duration of vomiting	0 day	4	22.2	3	13.0
	1 day	7	38.9	6	26.1
	2 days	6	33.3	4	17.4
	≥ 3 days	1	5.6	10	43.5
Maximum number of episodes of vomiting/24 hours	0	4	22.2	3	13.0
	1	4	22.2	3	13.0
	2-4	9	50.0	8	34.8
	≥ 5	1	5.6	9	39.1
Maximum fever reported/24 hours (measured rectally)	< 37.1°C	2	11.1	2	8.7
	37.1-38.4°C	5	27.8	7	30.4
	38.5-38.9°C	6	33.3	4	17.4
	≥ 39°C	5	27.8	10	43.5
Treatment	none	15	83.3	18	78.3
	Rehydration	2	11.1	5	21.7
	Hospitalization	1	5.6	0	0.0
Dehydration	none	17	94.4	20	87.0
	1-5%	1	5.6	3	13.0
	≥ 6%	0	0.0	0	0.0

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
N' = number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter SD= standard deviation
Comment: NA = not applicable

Supplement 34: Duration (in years) of the follow-up periods from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (total efficacy cohort)

Duration (years) of follow-up period	**HRV N=255**	**Placebo N=126**
Total	365.9	180.5
Mean	1.435	1.433
Minimum	0.016	0.121
Q1	1.414	1.414
Median	1.468	1.468
Q3	1.518	1.521
Maximum	1.595	1.584

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
Total = sum of follow-up period expressed in year
Q1 = 25th percentile Q3 = 75th percentile

Supplement 35: Percentage of subjects reporting RV GE and efficacy of the vaccine as measured by ELISA from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (total efficacy cohort)

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Any RV GE													
HRV	255	15	354.2	0.042	0.026	0.070	5.9	3.3	9.5	69.1	38.7	84.9	<0.001
Placebo	126	24	161.6	0.149	0.100	0.222	19.0	12.6	27.0				
Severe RV GE													
HRV	255	3	363.6	0.008	0.003	0.026	1.2	0.2	3.4	85.2	42.4	97.4	0.001
Placebo	126	10	172.4	0.058	0.031	0.108	7.9	3.9	14.1				

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified intensity, in each group
n/N = percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
n/T = person-year rate of RV GE episodes of the specified intensity in each group
95% CI = 95% confidence intervals p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 36: Percentage of subjects reporting severe RV GE and efficacy of the vaccine as measured by RT-PCR from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (total efficacy cohort)

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
Any RV GE													
HRV	255	17	349.3	0.049	0.030	0.078	6.7	3.9	10.5	61.8	24.7	81.0	0.002
Placebo	126	22	162.9	0.135	0.089	0.205	17.5	11.3	25.2				
Severe RV GE													
HRV	255	3	363.6	0.008	0.003	0.026	1.2	0.2	3.4	85.2	42.4	97.4	0.001
Placebo	126	10	172.4	0.058	0.031	0.108	7.9	3.9	14.1				

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified intensity, in each group
n/N = percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
n/T = person-year rate of RV GE episodes of the specified intensity in each group
95% CI = 95% confidence intervals p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 37: Percentage of subjects reporting RV GE (any intensity) and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by type (total efficacy cohort)

Type	Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI	
ELISA													
G1	HRV	255	12	357.0	0.034	0.019	0.059	4.7	2.5	8.1	71.8	39.9	87.3
	Placebo	126	21	164.9	0.127	0.083	0.195	16.7	10.6	24.3			
RT-PCR													
G1	HRV	255	16	350.3	0.046	0.028	0.075	6.3	3.6	10.0	62.4	24.3	81.6
	Placebo	126	21	164.9	0.127	0.083	0.195	16.7	10.6	24.3			
ELISA or RT-PCR													
G2	HRV	255	0	365.9	0.000	NE		0.0	0.0	1.4	100	-1827	100
	Placebo	126	1	179.4	0.006	0.001	0.040	0.8	0.0	4.3			
ELISA or RT-PCR													
G9	HRV	255	1	364.9	0.003	0.000	0.019	0.4	0.0	2.2	50.6	-3779	99.4
	Placebo	126	1	179.4	0.006	0.001	0.040	0.8	0.0	4.3			

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified type in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified type, in each group
n/N = percentage of subjects reporting at least one RV GE episode of the specified type in each group
n/T = person-year rate of RV GE episodes of the specified type in each group
NE = cannot be estimated 95% CI = 95% confidence intervals

Supplement 38: Percentage of subjects reporting severe RV GE and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by type (total efficacy cohort)

Type	Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI	
ELISA or RT-PCR													
G1	HRV	255	2	364.6	0.005	0.001	0.022	0.8	0.1	2.8	90.1	53.6	98.9
	Placebo	126	10	173.3	0.058	0.031	0.107	7.9	3.9	14.1			
ELISA or RT-PCR													
G2	HRV	255	0	365.9	0.000	NE		0.0	0.0	1.4	100	-1827	100
	Placebo	126	1	179.4	0.006	0.001	0.040	0.8	0.0	4.3			
ELISA or RT-PCR													
G9	HRV	255	1	364.9	0.003	0.000	0.020	0.4	0.0	2.2	infinity	infinity	98.7
	Placebo	126	0	180.5	0.000	NE		0.0	0.0	2.9			

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode of the specified type in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode of the specified type, in each group
n/N = percentage of subjects reporting at least one severe RV GE episode of the specified type in each group
n/T = person-year rate of severe RV GE episodes of the specified type in each group
NE = cannot be estimated 95% CI = 95% confidence intervals

Supplement 39: Percentage of subjects hospitalized due to any GE and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (total efficacy cohort)

			T	n / T			n / N			Vaccine efficacy			
Group	**N**	**n**	**(year)**	**rate**	**95% CI**		**%**	**95% CI**		**%**	**95% CI**		**p-value**
HRV	255	2	363.6	0.006	0.001	0.020	0.8	0.1	2.8	infinity	infinity	90.7	1.000
Placebo	126	0	180.5	0.000	NE		0.0	0.0	2.9				

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects hospitalized due to GE in each group
T = sum of follow-up period expressed in year censored at the first occurrence of hospitalization due to GE, in each group
n/N = percentage of subjects hospitalized due to GE in each group
n/T = person-year rate of hospitalization due to GE in each group
95% CI = 95% confidence intervals NE = cannot be estimated
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 40: Percentage of subjects reporting asymptomatic RV infection and efficacy of the vaccine from Visit 3 up to Visit 5 (end of the second efficacy follow-up period) (total efficacy cohort)

Group	N	n	%	95% CI		Vaccine efficacy %	95% CI		p-value
ELISA									
HRV	201	5	2.5	0.8	5.7	77.6	28.1	94.0	0.004
Placebo	90	10	11.1	5.5	19.5				
RT-PCR									
HRV	200	5	2.5	0.8	5.7	79.1	34.7	94.3	0.002
Placebo	92	11	12.0	6.1	20.4				

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group with available anti-rotavirus IgA antibody concentrations at visits 3 and 5 and who did not reported a rotavirus gastroenteritis episode between visits 3 and 5
n = number of subjects reporting asymptomatic RV infection in each group
% = percentage of subjects reporting asymptomatic RV infection in each group
95% CI = 95% confidence intervals p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 41: Percentage of subjects reporting any GE from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period and efficacy of the vaccine (total efficacy cohort)

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
HRV	255	165	223.3	0.739	0.634	0.861	64.7	58.5	70.6	0.6	-31.2	24.2	1.000
Placebo	126	82	107.3	0.764	0.615	0.949	65.1	56.1	73.4				

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one gastroenteritis episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of GE episode, in each group
n/N = percentage of subjects reporting at least one GE episode in each group
n/T = person-year rate of GE in each group
95% CI = exact 95% confidence intervals p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 42: Percentage of subjects reporting severe GE from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period and efficacy of the vaccine (total efficacy cohort)

Group	N	n	T (year)	n / T rate	95% CI		n / N %	95% CI		Vaccine efficacy %	95% CI		p-value
HRV	255	12	357.3	0.034	0.019	0.059	4.7	2.5	8.1	46.1	-34.8	78.2	0.168
Placebo	126	11	170.6	0.064	0.036	0.116	8.7	4.4	15.1				

Source: Appendix Tables IVA and VA

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe gastroenteritis episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe GE episode, in each group
n/N = percentage of subjects reporting at least one severe GE episode in each group
n/T = person-year rate of severe GE in each group
95% CI = exact 95% confidence intervals p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 43: Percentage of subjects in the HRV vaccine group reporting RV GE from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by status of anti-rotavirus IgA antibody concentration at Visit 3 (total efficacy cohort)

Anti-rotavirus IgA antibody status at Visit 3	N	n	%	95% CI	
ELISA					
Negative	47	6	12.8	4.8	25.7
Positive	187	7	3.7	1.5	7.6
Unknown	21	2	9.5	1.2	30.4
RT-PCR					
Negative	47	7	14.9	6.2	28.3
Positive	187	9	4.8	2.2	8.9
Unknown	21	1	4.8	0.1	23.8

Source: Appendix Tables IIIA, IVA and VA

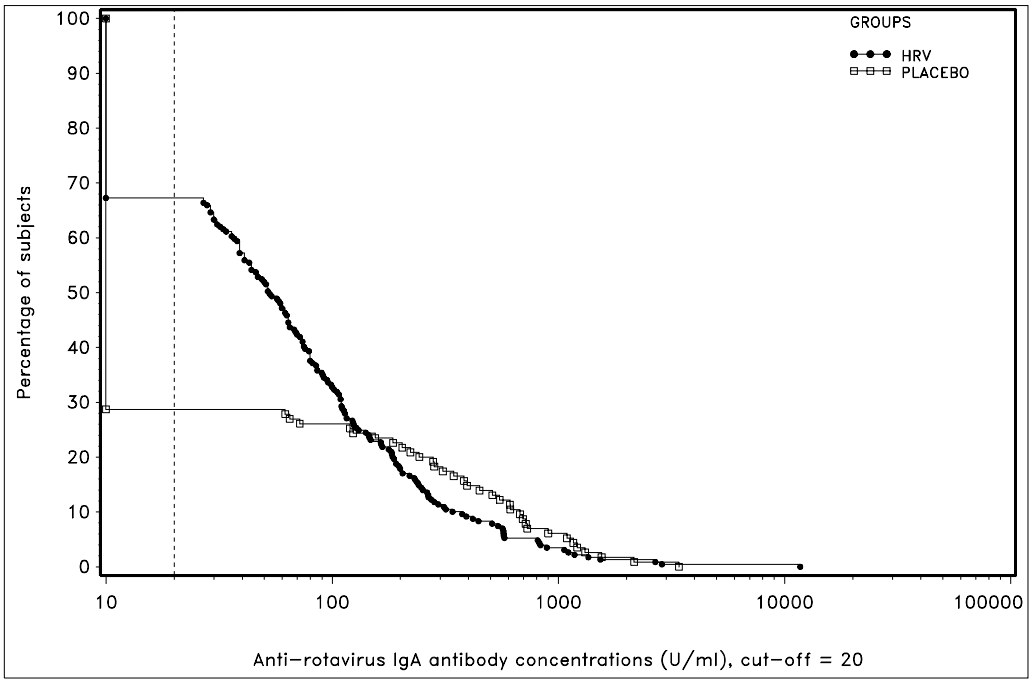
Notes: N = number of subjects included in the vaccine group with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 (Visit 3)
n/% = number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 reporting at least one RV GE episode on combined efficacy follow-up periods
95% CI = exact 95% confidence intervals

Supplement 44: Distribution of anti-rotavirus IgA antibody concentrations (total immunogenicity cohort)

Group	Timing	N	≥ 20 U/ml		≥ 40 U/ml		≥ 80 U/ml		≥ 160 U/ml		≥ 320 U/ml		≥ 640 U/ml		≥ 1280 U/l	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%
HRV	PRE	265	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	PII(M3)	234	187	79.9	179	76.5	162	69.2	134	57.3	97	41.5	59	25.2	23	9.8
	ES1	224	170	75.9	161	71.9	125	55.8	85	37.9	46	20.5	11	4.9	4	1.8
	ES2	229	154	67.2	131	57.2	90	39.3	53	23.1	24	10.5	12	5.2	5	2.2
Placebo	PRE	133	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	PII(M3)	122	1	0.8	1	0.8	1	0.8	1	0.8	1	0.8	1	0.8	0	0.0
	ES1	120	22	18.3	22	18.3	22	18.3	21	17.5	19	15.8	14	11.7	2	1.7
	ES2	115	33	28.7	33	28.7	30	26.1	27	23.5	20	17.4	12	10.4	4	3.5

Source: Appendix Table IIIA
Notes: N = number of subjects with available data
n/% = number/percentage of subjects with concentration above the specified range
Pre = Pre-vaccination PII(M3) = one month after the second vaccination
ES1 = end of the first RV season ES2 = end of the second RV season

Supplement 45: Reverse cumulative distribution curve for anti-rotavirus IgA antibody concentrations at Visit 5 at the end of the second RV season (total immunogenicity cohort)



Source: Appendix Table IIIA

Supplement 46: Anti-rotavirus IgA antibody GMCs and seropositivity rates for subjects with results available at all blood sampling timepoints (total iunogenicity cohort)

Group	Timing	N	≥ 20 U/ml				GMC (U/ml)				
					95% CI			95% CI		Range	
			n	%	L.L.	U.L.	Value	L.L.	U.L.	Min	Max
HRV	PRE	194	0	0.0	0.0	1.9	<20	NA	NA	<20	<20
	PII(M3)	194	153	78.9	72.4	84.4	176.9	137.5	227.4	<20	4161
	ES1	194	147	75.8	69.1	81.6	85.7	69.6	105.6	<20	3211
	ES2	194	138	71.1	64.2	77.4	60.5	49.1	74.6	<20	11749
Placebo	PRE	109	0	0.0	0.0	3.3	<20	NA	NA	<20	<20
	PII(M3)	109	0	0.0	0.0	3.3	<20	NA	NA	<20	<20
	ES1	109	18	16.5	10.1	24.8	20.2	14.9	27.5	<20	3014
	ES2	109	30	27.5	19.4	36.9	28.2	20.1	39.4	<20	3422

Source: Appendix Table IIIA

Notes: N = number of subjects with available data at all blood sampling timepoints
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval
L.L. = lower limit, U.L. = upper limit
Min = Minimum concentration
Max = Maximum concentration
Pre = Pre-vaccination
PII(M3) = one month after the second vaccination
ES1 = end of the first RV season
ES2 = end of the second RV season

Comment: NA = not applicable

Supplement 47: Distribution of anti-rotavirus IgA antibody concentrations for subjects with results available at all blood sampling timepoints (total immunogenicity cohort)

Group	Timing	N	≥ 20 U/ml		≥ 40 U/ml		≥ 80 U/ml		≥ 160 U/ml		≥ 320 U/ml		≥ 640 U/ml		≥ 1280 U/ml	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%
HRV	PRE	194	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	PII(M3)	194	153	78.9	151	77.8	140	72.2	120	61.9	88	45.4	55	28.4	22	11.3
	ES1	194	147	75.8	141	72.7	114	58.8	78	40.2	42	21.6	10	5.2	3	1.5
	ES2	194	138	71.1	119	61.3	85	43.8	49	25.3	22	11.3	11	5.7	5	2.6
Placebo	PRE	109	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	PII(M3)	109	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	ES1	109	18	16.5	18	16.5	18	16.5	17	15.6	15	13.8	13	11.9	1	0.9
	ES2	109	30	27.5	30	27.5	27	24.8	25	22.9	19	17.4	11	10.1	4	3.7

Source: Appendix Table IIIA

Notes: N = number of subjects with available data at all blood sampling timepoints
n/% = number/percentage of subjects with concentration above the specified range
Pre = Pre-vaccination
PII(M3) = one month after the second vaccination
ES1 = end of the first RV season
ES2 = end of the second RV season

Supplement 48: Anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies for subjects with results available at all blood sampling timepoints (total immunogenicity cohort)

Group	Timing	N	GMC (U/ml)				
				95% CI		Range	
			Value	L.L.	U.L.	Min	Max
HRV	PII(M3)	153	381.9	321.0	454.4	28	4161
	ES1	147	170.4	146.0	198.8	24	3211
	ES2	138	125.7	104.6	151.0	27	11749
Placebo	ES1	18	714.4	493.2	1034.7	116	3014
	ES2	30	430.8	296.4	626.0	62	3422

Source: Appendix Table IIIA

Notes: N = number of subjects with available data at all blood sampling timepoints and who were seropositive for anti-rotavirus IgA antibodies
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% confidence interval
L.L. = lower limit, U.L. = upper limit
Min = Minimum concentration
Max = Maximum concentration
PII(M3) = one month after the second vaccination
ES1 = end of the first RV season
ES2 = end of the second RV season

Appendix A: Clintrial Eligibility Codes

Elimination from ATP analysis of safety, immunogenicity and efficacy (E)

1010 Subject or vaccine number not allocated
HRV vaccine or placebo not administered at all
No subject allocated to the randomized number

1030 Study vaccine dose not administered but subject number allocated
HRV vaccine or placebo not administered at all

1040 Administration of vaccine(s) forbidden in the protocol

1050 Randomization failure
Replacement vial used in double-blind studies in with replacement dose are unique whatever the vaccine group
Wrong vaccine vial given
Subject number not in the randomization list and not requested by the sponsor (extra subject)

1060 Randomization code broken at the investigator site (for double-blind studies)

1070 HRV or placebo dose not administered according to protocol

1080 Essential data missing
Date of vaccination unknown
No info on solicited or unsolicited symptoms available: all is missing

1500 Initially positive or unknown status for rotavirus on the day of Dose 1

Elimination from ATP analysis of immunology (I)

2010 Protocol violation (any inclusion/exclusion criteria not met at study entry)
Ex : Demographics : Too young
Too old
Unknown age
Underlying medical condition forbidden by the protocol at screening /
Medical history

2040 Administration of any medication forbidden by the protocol

2050 Underlying medical condition forbidden by the protocol during the study

2060 Concomitant infection by rotavirus which may influence immune response

2070 Concomitant infection not related to the vaccine which may influence immune response

2080 Non compliance with vaccination schedule (including wrong and unknown dates)
Not assigned if code 2100 or 2110 has been assigned

2090 Non compliance with blood sample schedule (including wrong and unknown dates)
Not assigned if code 2100 or 2110 has been assigned

2100 Essential serological data missing

Essential blood sample lost
Essential blood sample unable to test (hemolysis, insufficient volume, ...)
Essential blood sample not done
Absence of parallelism

2110 Essential serological data temporarily missing because of not yet tested (interim analysis)

2120 Obvious incoherence, abnormal serology evolution or error in data (incoherence between CRF and results)
Wrong labeling in BS

2130 Subject not planned in the protocol to be bled for their all blood sampling visits (and effectively not bled)

2500 Others

Elimination from ATP analysis of Efficacy – first and combined follow-up periods

3010 At least one study vaccine dose not administered

3020 Subjects not entered into the surveillance period of the first efficacy follow-up period

3030 Concomitant infection by rotavirus up to 2 weeks after Dose 2 which may influence efficacy response

Elimination from ATP analysis of Efficacy – second follow-up periods

4020 Subjects not entered into the surveillance period of the second efficacy follow-up period

Appendix B: Notes to Appendices

Sub. No.	:	subject number
Ctr	:	center number
Elig	:	Eligibility
E	:	Elimination from reactogenicity analysis
I	:	Elimination from immunogenicity analysis
Elim	:	Eliminated from analysis(es)
F	:	Female
M	:	Male

Appendix IC

Pre	:	Pre vaccination blood sampling
PII(M3)	:	Post vaccination blood sample taken one month after the second vaccination at Month 3
PII(M12)	:	Blood sample taken at the end of first RV season
PII(M24)	:	Blood sample taken at the end of second RV season
VIS ND	:	Visit not done
BS ND	:	Blood sampling not done

Appendix ID

past	:	medical history
current	:	present at the physical examination
Both	:	past and current

Appendix IE

Elim Crit	:	elimination criteria during the study Y/N: Yes/No

Appendix IIB

G?	:	Any solicited general symptom reported? Y / N: Yes / No
Exp	:	Adverse experience: Y / N: Yes / No
O?	:	Ongoing at day 14? Y / N: Yes / No
Last day	:	End day of symptom if it has continued after the solicited follow-up period
RTE	:	Route (for body temperature recording):
O	=	Oral
A	=	Axillary
R	=	Rectal
T	=	Tympanic
caus	:	causality : Yes = Related No = Not related

Symptoms

DA	:	Diarrhea
IR	:	Irritability/fussiness
LO	:	Loss of appetite
TE	:	Temperature
VO	:	Vomiting

IR scored as

Empty / 0	:	Behavior as usual

1	:	Crying more than usual/no effect on normal activity
2	:	Crying more than usual/interferes with normal activity
3	:	Crying that cannot be comforted/prevents normal activity

DA recorded as number of looser than normal stools
VO recorded as number of vomiting episodes
LO scored as

Empty / 0	:	Normal
1	:	Eating less than usual/no effect on normal activity
2	:	Eating less than usual/interferes with normal activity
3	:	Not eating at all

Appendix IICi and IICii

Verbatim	:	Description of event as recorded in the case report form
Keyword	:	Specific identification terminology linked to WHO classification codes
WHO code	:	Code for WHO preferred term, a WHO adverse reaction classification system
Preferred term	:	Medical term assigned to the keyword/verbatim
Body syst	:	Numeric code in relation with the location of the adverse event in the body
PrDo	:	Vaccine dose administered prior to the adverse event
caus	:	Causality yes = Related no = Not related
Start date	:	Date of onset of adverse event
Day onset	:	Number of days since last vaccine dose
End date	:	Date of end of adverse event
Dur (d)	:	Duration (days)
Int	:	Intensity scored as:
Empty / 0	:	Absent
1	:	The adverse event was easily tolerated, causing minimal discomfort and not interfering with everyday activities.
2	:	The adverse event was sufficiently discomforting to interfere with normal everyday activities.
3	:	An adverse event which prevented normal, everyday activities.
L/G	:	Local or General
Out	:	Outcome: 1 = recovered 2 = recovered with sequelae 3 = ongoing 4 = died 5 = unknown
Ser	:	Serious adverse event: N / Y = No / Yes
AEGIS No.	:	GlaxoSmithKline Biologicals' code for case identification of serious adverse event

Appendix IIDi

Prev. dose	:	previous vaccine dose
Rel. day of onset	:	day of onset of medication, relative to day of previous vaccination
Start date	:	Date of start of medication
End date	:	Date of end of medication
DUR(d)	:	Duration (days)
Code	:	Treatment code; a direct link was recorded between the adverse event and the medication
Trade-Generic name	:	trade and/or generic name of medication
Medical indic.	:	medical indication for which medication was used
Proph	:	Prophylactic medication Y (Yes) or blank

Appendix IIDii

Prev. dose	:	previous vaccine dose
Rel. day of onset	:	day of onset of concomitant vaccination, relative to day of previous vaccination
Vaccination date	:	date of administration of previous study vaccine
Start date	:	date of administration of concomitant vaccine
Trade name	:	trade name of vaccine administered

Appendix IIIA

cut	:	Cut-off of the laboratory assay
Pre	:	Pre vaccination blood sampling
PII(M3)	:	Post vaccination blood sample taken one month after the second vaccination at Month 3
PII(M12)	:	Blood sample taken at the end of first RV season
PII(M24)	:	Blood sample taken at the end of second RV season
BS ND	:	Blood sample not done
IR	:	Invalid result
QNS	:	Quantity not sufficient

Appendix IVA

Epis nb	:	Episode number
MC	:	Missing confirmed
NEG	:	Negative for rotavirus
POS	:	Positive for rotavirus
ND	:	Not done
IR	:	Invalid result
QNS	:	Quantity not sufficient

Appendix VA

NEG	:	Negative for rotavirus
POS	:	Positive for rotavirus
QNS	:	Quantity not sufficient

Appendix C: Mathematical details about the computation of the 95% CI for vaccine efficacy*

The Vaccine Efficacy (VE) can be estimated by:

$$VE = 1 - \frac{n1/N1}{n2/N2} = 1 - \frac{n1}{r * n2}$$

where n1 = number of cases in the vaccine group
N1 = number of subjects in the vaccine group
n1 = number of cases in the placebo group
N2 = number of subjects in the placebo group
r = $\frac{N1}{N2}$

Conditionally to the total number of cases n = n1+ n2 and r, let *p* denote the proportion of cases in the vaccine group,

$$VE = 1 - \frac{n1}{n} * \frac{n}{r * (n - n1)} = 1 - p * \frac{1}{r * (1 - p)} = 1 - \frac{p}{r * (1 - p)}$$

where $p = n1/n$ is binomially distributed

There is therefore a monotonic link between VE, the true vaccine efficacy, and p, the true proportion of subjects in the vaccine group among the total cases in the two groups.

95% CI for vaccine efficacy can then be derived from the exact 95% CI from p.

* V. Dragalin, V. Fedorov and B. Cheuvart. Statistical approaches to establishing vaccine safety. Statistics in medicine 2002; 21:877-893

Study Report 444563/004 (rota-004)

Erratum Sheet for the final report dated April 30, 2003 and the annex report dated November 14, 2003

Reason for the Erratum:

In the final report dated 30 April 2003 and the annex report dated November 14, 2003, there were either missing results or inconsistencies between the ELISA and RT-PCR data for gastroenteritis (GE) stool analysis for six subjects.

[redacted]

The rule followed for the repeat tests was as follows: when the repeat test confirmed the results of the first test, the result was considered as the final result. When the repeat test did not confirm the results of the first test, a second repeat was done and the correct result was the result obtained twice.

The corrected ELISA and RT-PCR results were as follows:

For the first efficacy follow-up period after vaccination

- [redacted]
- [redacted]

For the second efficacy follow-up period after vaccination

- [redacted]
- [redacted]

- [redacted]

For the combined efficacy follow-up periods after vaccination
[redacted]

Calculations pertaining to the main objectives of the study, i.e. vaccine efficacy, were redone and the results of the reanalysis with the corrected test results are presented in this Erratum.

Although the efficacy estimates are slightly higher, the changes do not alter the study conclusions. The corrected results were included in a manuscript submitted to BMJ.

The changes are highlighted in *bold italic* font.

Analysis of efficacy during the first efficacy follow-up period after vaccination

The following tables in the final report dated 30 April 2003 were amended. Table numbers stated below are the same as the respective tables in the final report dated 30 April 2003.

Table 13: Percentage of subjects reporting RV GE and efficacy of the vaccine as measured by ELISA during the first efficacy follow-up period (ATP efficacy cohort)

Group	N	n	n / N rate	95%CI		Vaccine efficacy %	95%CI		p-value
Any RV GE									
HRV	245	***7***	***2.9***	***1.2***	***5.8***	***73.0***	***27.1***	***90.9***	***0.003***
Placebo	123	13	10.6	5.7	17.4				
Severe RV GE									
HRV	245	1	0.4	0.0	2.3	90.0	10.3	99.8	0.017
Placebo	123	5	4.1	1.3	9.2				

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
n/N= percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
95%CI = 95%confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Table 14: Percentage of subjects reporting RV GE and efficacy of the vaccine as measured by RT-PCR during the first efficacy follow-up period (ATP efficacy cohort)

Group	N	n	n / N rate	95%CI		Vaccine efficacy %	95%CI		p-value
Any RV GE									
HRV	245	12	4.9	2.6	8.4	***53.7***	***-10.2***	***80.7***	***0.049***
Placebo	123	***13***	***10.6***	***5.7***	***17.4***				
Severe RV GE									
HRV	245	1	0.4	0.0	2.3	90.0	10.3	99.8	0.017
Placebo	123	5	4.1	1.3	9.2				

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
n/N= percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
95%CI = 95%confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Analysis of efficacy during the second efficacy follow-up period after vaccination

The following tables in the annex report dated November 14, 2003 were amended. Table and Supplement numbers stated below are the same as the respective tables and supplements in the annex report dated November 14, 2003.

Table 5: Percentage of subjects reporting RV GE (any and severe intensity) and efficacy of the vaccine as measured by ELISA during the second efficacy follow-up period (ATP efficacy cohort)

Group	N	n	T (year)	n / T value	95%CI		n / N rate	95%CI		Vaccine efficacy %	95%CI		p-value
Any RV GE													
HRV	241	***6***	***237.0***	***0.025***	***0.011***	***0.056***	***2.5***	***0.9***	***5.3***	***72.8***	***19.9***	***91.8***	***0.007***
Placebo	120	***11***	***115.5***	***0.095***	***0.053***	***0.172***	***9.2***	***4.7***	***15.8***				
Severe RV GE													
HRV	241	2	237.7	0.008	0.002	0.034	0.8	0.1	3.0	83.4	7.2	98.4	0.018
Placebo	120	6	116.8	0.051	0.023	0.114	5.0	1.9	10.6				

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified intensity in the second efficacy follow-up period, in each group
n/N= percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
n/T= person-year rate of RV GE of the specified intensity in each group
95%CI= 95%confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Table 6: Percentage of subjects reporting RV GE (any and severe intensity) and efficacy of the vaccine as measured by RT-PCR during the second efficacy follow-up period (ATP efficacy cohort)

Group	N	n	T (year)	n / T value	95%CI		n / N rate	95%CI		Vaccine efficacy %	95%CI		p-value
Any RV GE													
HRV	241	6	237.0	0.025	0.011	0.056	2.5	0.9	5.3	***72.8***	***19.9***	***91.8***	***0.007***
Placebo	120	***11***	***115.5***	***0.095***	***0.053***	***0.172***	***9.2***	***4.7***	***15.8***				
Severe RV GE													
HRV	241	2	237.7	0.008	0.002	0.034	0.8	0.1	3.0	83.4	7.2	98.4	0.018
Placebo	120	6	116.8	0.051	0.023	0.114	5.0	1.9	10.6				

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified intensity in the second efficacy follow-up period, in each group
n/N= percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
n/T= person-year rate of RV GE of the specified intensity in each group
95%CI= 95%confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 5: Percentage of subjects reporting RV GE (any intensity) and efficacy of the vaccine during the second efficacy follow-up period, by type (ATP efficacy cohort)

Group	N	n	T (year)	n / T value	95%CI		n / N rate	95%CI		Vaccine efficacy %	95%CI	
ELISA or RT-PCR G1 type												
HRV	241	5	238.0	0.021	0.009	0.050	2.1	0.7	4.8	***77.4***	***29.3***	***93.8***
Placebo	120	***11***	***115.5***	***0.095***	***0.053***	***0.172***	***9.2***	***4.7***	***15.8***			
ELISA or RT-PCR G9 type												
HRV	241	1	237.8	0.004	0.001	0.030	0.4	0.0	2.3	-infini	-infini	98.7
Placebo	120	0	119.4	0.000	NE		0.0	0.0	3.0			

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified intensity in the second efficacy follow-up period, in each group
n/N = percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
n/T = person-year rate of RV GE symptom of the specified intensity in each group
NE = can not be estimated 95%CI= 95%confidence intervals

Supplement 8: Percentage of subjects in the HRV vaccine group reporting RV GE during the second efficacy follow-up period, by status of anti-rotavirus IgA antibody concentration at Visit 3 (ATP efficacy cohort)

Anti-rotavirus IgA antibody status at Visit 3	N	n	%	95%CI	
ELISA					
Negative	45	2	4.4	0.5	15.2
Positive	180	4	2.2	0.6	5.6
Unknown	16	***0***	***0.0***	***0.0***	***20.6***
RT-PCR					
Negative	45	2	4.4	0.5	15.2
Positive	180	4	2.2	0.6	5.6
Unknown	16	0	0.0	0.0	20.6

Source: Appendix Tables IIIA, IVA and VA
Notes: N = number of subjects included in the vaccine group with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 (Visit 3)
n/% = number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 reporting at least one RV GE episode during the second efficacy follow-up period
95%CI = exact 95% confidence intervals

Analysis of efficacy over two consecutive efficacy follow-up periods after vaccination

The following tables in the annex report dated November 14, 2003 were amended. Table and Supplement numbers stated below are the same as the respective tables and supplements in the annex report dated November 14, 2003.

Table 9 shows the vaccine efficacy against any and severe RV GE for the combined efficacy follow-up period. The vaccine efficacy against any RV GE was changed to 71.6 % (instead of 68.6 %) according to the corrected values. There was no change for the efficacy against "severe" RV GE. Table 10 shows the corresponding results as obtained by RT-PCR. Again, the vaccine efficacy against any RV GE was changed (from 61.2% to 62.9%) but there was no change for the efficacy against severe RV GE.

Table 9: Percentage of subjects reporting RV GE (any and severe intensity) and efficacy of the vaccine as measured by ELISA from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (ATP efficacy cohort)

Group	N	n	T (year)	n / T value	95%CI		n / N rate	95%CI		Vaccine efficacy %	95%CI		p-value
Any RV GE													
HRV	245	***13***	***342.3***	***0.038***	***0.022***	***0.065***	***5.3***	***2.9***	***8.9***	***71.6***	***41.6***	***86.8***	***<0.001***
Placebo	123	***23***	***157.9***	***0.146***	***0.097***	***0.219***	***18.7***	***12.2***	***26.7***				
Severe RV GE													
HRV	245	3	349.8	0.009	0.003	0.027	1.2	0.3	3.5	84.9	41.5	97.3	0.001
Placebo	123	10	168.1	0.059	0.032	0.111	8.1	4.0	14.4				

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified intensity in each group
n/N= percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
n/T= person-year rate of RV GE of the specified intensity in each group
95%CI= 95%confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Table 10: Percentage of subjects reporting RV GE (any and severe intensity) and efficacy of the vaccine as measured by RT-PCR from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period (ATP efficacy cohort)

Group	N	n	T (year)	n / T value	95%CI		n / N rate	95%CI		Vaccine efficacy %	95%CI		p-value
Any RV GE													
HRV	245	17	335.5	0.051	0.031	0.082	6.9	4.1	10.9	***62.9***	***27.4***	***81.4***	***0.001***
Placebo	123	***23***	***157.9***	***0.146***	***0.097***	***0.219***	***18.7***	***12.2***	***26.7***				
Severe RV GE													
HRV	245	3	349.8	0.009	0.003	0.027	1.2	0.3	3.5	84.9	41.5	97.3	0.001
Placebo	123	10	168.1	0.059	0.032	0.111	8.1	4.0	14.4				

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified intensity in each group
n/N= percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
n/T= person-year rate of RV GE of the specified intensity in each group
95%CI= 95%confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 25: Percentage of subjects reporting RV GE (any intensity) and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by type (ATP efficacy cohort)

Group	N	n	T (year)	n / T value	95%CI		n / N rate	95%CI		Vaccine efficacy %	95%CI	
ELISA G1 type												
HRV	245	12	343.2	0.035	0.020	0.062	4.9	2.6	8.4	***72.6***	***42.2***	***87.6***
Placebo	123	***22***	***159.9***	***0.138***	***0.091***	***0.209***	***17.9***	***11.6***	***25.8***			
RT-PCR G1 type												
HRV	245	16	336.5	0.048	0.029	0.078	6.5	3.8	10.4	***63.5***	***27.2***	***82.1***
Placebo	123	***22***	***159.9***	***0.138***	***0.091***	***0.209***	***17.9***	***11.6***	***25.8***			
ELISA / RT-PCR G2 type												
HRV	245	0	352.1	0.000	NE		0.0	0.0	1.5	100	-1858	100
Placebo	123	1	175.0	0.006	0.001	0.040	0.8	0.0	4.4			
ELISA / RT-PCR G9 type												
HRV	245	1	351.1	0.003	0.000	0.020	0.4	0.0	2.3	49.8	-3841	99.4
Placebo	123	1	175.1	0.006	0.001	0.041	0.8	0.0	4.4			

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of the specified intensity in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of the specified intensity in each group
n/N = percentage of subjects reporting at least one RV GE episode of the specified intensity in each group
n/T = person-year rate of RV GE of the specified intensity in each group
NE = can not be estimated 95%CI= 95%confidence intervals

Table 12: Percentage of subjects reporting asymptomatic RV infection and efficacy of the vaccine from one month after Dose 2 up to the second RV season time point (ATP efficacy cohort)

Group	N	n	%	95%CI		Vaccine efficacy %	95%CI		p-value
ELISA									
HRV	***195***	4	2.1	0.6	5.2	***81.9***	***37.4***	***95.9***	0.002
Placebo	***88***	10	***11.4***	***5.6***	***19.9***				
RT-PCR									
HRV	193	4	2.1	0.6	5.2	***81.8***	***36.8***	***95.8***	***0.002***
Placebo	***88***	***10***	***11.4***	***5.6***	***19.9***				

Source: Appendix Tables IVA and VA
Notes: N = number of subjects included in each group with available anti-rotavirus IgA antibody concentrations at Visits 3 and 5 and who did not reported a RV GE episode between Visits 3 and 5
n = number of subjects reporting asymptomatic RV infection in each group
% = percentage of subjects reporting asymptomatic RV infection in each group
95%CI = exact 95%confidence intervals
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 28: Percentage of subjects in the HRV vaccine group reporting RV GE from 2 weeks after Dose 2 up to the end of the second efficacy follow-up period, by status of anti-rotavirus IgA antibody concentration at Visit 3 (ATP efficacy cohort)

Anti-rotavirus IgA antibody status at Visit 3	**N**	**n**	**%**	**95%CI**	
ELISA					
Negative	45	6	13.3	5.1	26.8
Positive	181	***6***	***3.3***	***1.2***	***7.1***
Unknown	19	***1***	***5.3***	***0.1***	***26.0***
RT-PCR					
Negative	45	7	15.6	6.5	29.5
Positive	181	9	5.0	2.3	9.2
Unknown	19	1	5.3	0.1	26.0

Source: Appendix Tables IIIA, IVA and VA

Notes: N = number of subjects included in the vaccine group with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 (Visit 3)
n/% = number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration one month after Dose 2 reporting at least one RV GE episode during the second efficacy follow-up period
95%CI = exact 95% confidence intervals

Supplements A, Supplement B and Supplement C are provided in the erratum as a summary of all the RV GE cases reported during the study. The corrected results are highlighted in bold-italics.

Supplement A: List of subjects with RV GE (by ELISA and RT-PCR) from 2 weeks after Dose 2 till end of the first RV season

Subject	Group	Start of the GE	Onset*	ELISA	RT-PCR	G type	Score
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.							

*Onset = number of days between the start of the GE and Dose 2
Comment: [redacted]

Supplement B: List of subjects with RV GE (by ELISA and RT-PCR) from end of the first RV season (Visit 4) till end of the second RV season

Subject	Group	Start of the GE	Onset*	ELISA	RT-PCR	G type	Score

This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.

*Onset = number of days between the start of the GE and Dose 2
Comment:

Supplement C: List of subjects with RV GE (by ELISA and RT-PCR) from 2 weeks after Dose 2 till end of the second RV season

Subject	Group	Start of the GE	Onset*	ELISA	RT-PCR	G type	Score
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the Sponsor Clinical Study Register.							

*Onset = number of days between the start of the GE and Dose 2
Comment:

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

CONFIDENTIAL

Final Study Report for Clinical Trial 444563/006 (rota-006)

Title: A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with HRV, when administered concurrently with DTPw-HBV and Hib vaccines.

Study vaccines:	GSK Biologicals' live attenuated human rotavirus vaccine.
CPMS Study No.:	444563/006 (rota-006)
Indication:	Two oral doses at two months interval to healthy infants, 2 months (6–12 weeks) of age at the time of Dose 1.
Principal Investigators:	Dr. [redacted] M.D., Brazil Dr. [redacted] M.D., Mexico Dra. [redacted] M.D., Venezuela Dra. [redacted] Ph.D as the Principal Study Co-ordinator for Venezuela
Date of First Visit:	May 25, 2001
Data Lock Point:	April 24, 2003
Coordinating Author:	[redacted] Scientific Writer
Contributing authors:	[redacted] Biometrician [redacted] Director [redacted] Central Study Coordinator [redacted] Clinical Development Manager [redacted] Biometrician

The trial was performed according to the Good Clinical Practice guidelines in operation at the time of the initiation of the trial.

Report Date: November 14, 2003

Synopsis of Final Report for Clinical Trial 444563/006 (rota-006)

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Title of the study: A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ foci forming units (ffu)) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with HRV, when administered concurrently with DTPw-HBV and Hib vaccines.

Principal Investigators: [redacted] M.D., Brazil
[redacted] M.D., Mexico
Dra. [redacted] M.D., Venezuela
Dra. [redacted] Ph.D as the Principal Study Co-ordinator for Venezuela

Study sites: This multicentre trial was conducted in Brazil, Mexico and Venezuela.

Publications:

- Protective efficacy of an oral HRV vaccine in Latin American infants. Poster presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Diego, USA, September 27–30, 2002.
- Immunogenicity and reactogenicity of an oral HRV vaccine in Latin American infants. Poster presented at the World Society for Pediatric Infectious Diseases (WSPID), Santiago, Chile, November 18–21, 2002.
- Impact of maternal antibodies on the immune response to an oral human rotavirus (HRV) vaccine in Mexican infants. Poster presented at the WSPID, Santiago, Chile, November 18–21, 2002.
- Efficacy of two doses of a human monovalent rotavirus vaccine, Rotarix®, in preventing gastro-enteritis due to G1 and non-G1 rotavirus in Brazil, Mexico and Venezuela. Oral communication at the 8th International Symposium on DS-RNA Viruses, Lucca, Italy, September 13–18, 2003.

Study period: Date of first visit: May 25, 2001 Data lock point: April 24, 2003	**Clinical phase:** IIb

Note: Although all study objectives and endpoints are listed, this study report only presents the efficacy, safety and immunogenicity obtained during the first efficacy follow-up period. An annex report will present results obtained during the second efficacy follow-up period.

Objectives: Primary:

For the subset of subjects who were planned to receive two doses of HRV or placebo:

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine, to demonstrate the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations in preventing any rotavirus (RV) gastroenteritis (GE) during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period.

Secondary:

First efficacy follow-up period

For the subset of subjects planned to receive two doses of HRV or placebo:

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

vaccine, to assess if two doses of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations can:

- Prevent severe RV GE during-the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Prevent RV GE due to virus types heterologous to vaccine strain from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Prevent any and severe pure RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Prevent mixed RV GE (GE associated with RV and at least one other pathogen) during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Prevent any hospitalization for RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.

For the subset of subjects who received three dose of HRV or placebo:

- To explore the rates of any and severe RV GE during the period starting from 2 weeks after Dose 3 until the end of the first efficacy follow-up period.

Second efficacy follow-up period (for a subset of approximately 1000 subjects)

- To evaluate the efficacy of the HRV vaccine during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period, and during the period starting from 2 weeks after the last HRV/placebo dose until the end of the second efficacy follow-up period.

Safety/Reactogenicity

- To assess the safety and reactogenicity of two doses of GSK Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo.
- To assess the safety and reactogenicity of the third dose of GSK Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo in a subset of subjects.

Immunogenicity

For the subset of subjects who were planned to receive two doses of HRV or placebo:

- To assess vaccine take, in subjects previously uninfected with RV before vaccination, two months after each study vaccine dose in the stool analysis subset (subjects with at least one available result for stools collected at pre-determined timepoints). Vaccine take was defined as the appearance of serum IgA to RV in post-immunization sera at a concentration ≥ 20 U/ml and/or vaccine virus shedding in any stool sample collected from Visit 1 to Visit 3.
- To assess persistence of serum IgA to RV at the end of the first efficacy follow-up period.
- To explore in a subset of subjects effect of GSK Biologicals' HRV vaccine on the immune response to concurrently administered routine vaccinations.
- To explore the effect of unrestricted feeding on the immunogenicity of the vaccine.
- To assess viral shedding in the vaccine groups in the stool analysis subset.

For the subset of subjects who received three doses of HRV or placebo:

- To assess serum IgA to RV, two months after Dose 2 and Dose 3 of HRV vaccine or placebo.
- To assess viral shedding in the vaccine groups after the third HRV vaccine dose.
- To explore the effect of GSK Biologicals' HRV vaccine on the immune response to concurrently administered routine vaccinations two months after the third dose of routine vaccines.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Methodology:
Study design: Double-blind, randomized, placebo-controlled study with four parallel groups with balanced allocation (1:1:1:1). Two oral doses were administered according to a 0, 2 month schedule to healthy infants who were 2 months of age at the time of Dose 1 of HRV vaccine or placebo. A subset of subjects received a third dose of the HRV vaccine or placebo at 6 months of age. No restrictions on feeding the infants before or after study vaccine or placebo administration. Hepatitis B, Bacillus Calmette-Guerin (BCG) and oral polio vaccine (OPV) vaccinations at birth were allowed according to local Expanded Program of Immunization (EPI). For the subset planned to receive two doses of HRV vaccine or placebo, routine vaccinations [diphtheria-tetanus-whole-cell pertussis-hepatitis B-*Haemophilus influenzae* type b vaccine (DTPw-HB+Hib vaccine)] were to be administered concomitantly with the study vaccines at 2 and 4 months of age; thereafter, DTPw-HB+Hib vaccine was to be given at 6 months of age. Subjects planned to receive three doses of HRV vaccine or placebo were to receive the routine vaccinations concomitantly with each dose of HRV vaccine or placebo. OPV was to be given at the discretion of the investigator, but was not to be administered during the period starting 2 weeks before each dose of study vaccine and ending 2 weeks after.

Number of subjects:

Planned study enrolment: 2640 **Amended target enrolment:** 2276
Total number of subjects enrolled: 2276 **Completed Visit 4:** 2125

Subset planned to receive two doses of HRV vaccine or placebo

Enrolled: 2155 Completed Visit 4: 2004 (Of the 151 drop outs, 3 were due to unrelated Serious Adverse Events (SAEs) and 6 were due to non-serious adverse events (AEs))

Analyzed for efficacy during the 1st efficacy follow-up period:

Total vaccinated cohort: 2044 subjects (507 in $10^{4.7}$ ffu HRV group, 508 in $10^{5.2}$ ffu HRV group, 512 in $10^{5.8}$ ffu HRV group and 517 in placebo group)

According to protocol (ATP) cohort: 1846 subjects (468 in $10^{4.7}$ ffu HRV group, 460 in $10^{5.2}$ ffu HRV group, 464 in $10^{5.8}$ ffu HRV group and 454 in placebo group)

Analyzed for safety:

Total vaccinated cohort: 2155 subjects (538 in $10^{4.7}$ ffu HRV group, 540 in $10^{5.2}$ ffu HRV group, 540 in $10^{5.8}$ ffu HRV group and 537 in placebo group)

ATP cohort: 1965 subjects (499 in $10^{4.7}$ ffu HRV group, 487 in $10^{5.2}$ ffu HRV group, 493 in $10^{5.8}$ ffu HRV group and 486 in placebo group).

Analyzed for immunogenicity:

Total vaccinated cohort: 2151 subjects (537 in $10^{4.7}$ ffu HRV group, 535 in $10^{5.2}$ ffu HRV group, 540 in $10^{5.8}$ ffu HRV group and 539 in placebo group).

ATP cohort: 1526 subjects (395 in $10^{4.7}$ ffu HRV group, 377 in $10^{5.2}$ ffu HRV group, 381 in $10^{5.8}$ ffu HRV group and 373 in placebo group).

Subset receiving three doses of HRV vaccine or placebo

Enrolled and included in the total vaccinated cohort for analysis of efficacy, safety and immunogenicity: 121 Completed Visit 4: 121

Diagnosis and criteria for inclusion: Healthy infants, born after a normal gestation period of 36–42 weeks or with a birth weight > 2000 g, 6–12 weeks of age at the time of the first dose of HRV vaccine or placebo, free of obvious health problems as established by medical history and clinical examination before entering into the study, and with written informed consent obtained from parents or guardians of the subject.

444563/006 Synopsis page 3 of 12

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Test product, dose, mode of administration, lot numbers:

- One dose of GSK Biologicals' lyophilized HRV vaccine contained $10^{4.7}$ ffu, $10^{5.2}$ ffu or $10^{5.8}$ ffu of HRV strain, RIX4414 derived from the 89-12 HRV vaccine strain, 9 mg sucrose, 18 mg dextran, 13.5 mg sorbitol and 9 mg amino acids. Lot numbers: DRVC005A46 for HRV vaccine $10^{4.7}$ ffu, DRVC010A48 for HRV vaccine $10^{5.2}$ ffu and DRVC004A46 for HRV vaccine $10^{5.8}$ ffu. Lot numbers 00J03/1010, 00I19/1006, 00J03/1010, 00J04/1011 and 01C09/1013 were used for the diluent (calcium carbonate 60 mg/ml and xanthane 0.25 % in 1 ml water for injection).

Mode of administration: Lyophilized HRV vaccine was reconstituted with the supplied diluent and the resuspended product was administered as a single oral dose.

Reference therapy, dose and mode of administration, lot numbers:

- One dose of GSK Biologicals' lyophilized placebo for HRV vaccine contained 9 mg sucrose, 18 mg dextran, 13.5 mg sorbitol and 9 mg amino acids. Lot numbers: DRVC014A48PL and DRVC006A46PL.
  Lot numbers 00J03/1010, 00I19/1006, 00J03/1010, 00J04/1011 and 01C09/1013 were used for the diluent (calcium carbonate 60 mg/ml and xanthane 0.25 % in 1 ml water for injection).

Mode of administration: Lyophilized placebo was reconstituted with the supplied diluent and the resuspended product was administered as a single oral dose.

Duration of study: For the subjects who participated only in the first efficacy follow-up period (until age 12 months), the intended duration of the study, per subject, was approximately 10 months. For the subset of subjects who participated in a second efficacy follow-up period (until maximum age 24 months), the intended duration of the study, per subject, was 22 months at most.

Criteria for evaluation:

Efficacy: Recording of rectal/axillary temperature, number of vomiting episodes, number of looser than normal stools passed by the subject, treatment administered and any dehydration during each suspected episode of GE (defined as diarrhea) occurring during the study.
Collection of stool samples during each diarrheal episode for RV detection by Enzyme Linked Immunosorbent Assay (ELISA). RV type was determined by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR). Episodes were counted as distinct events only if there were 5 or more symptom-free days between the episodes. A 20-point scoring system was used to assess the severity of each GE episode (Ruuska T and Vesikari T, Scand J Infect Dis 1990;22:259–67). A score of < 7 was prospectively defined as mild, a score of 7–10 was prospectively defined as moderate and a score ≥ 11 was prospectively defined as severe (Joensuu J *et al*, Lancet 1997;350:1205–9).

***Primary endpoint*:**

For the subset of subjects planned to receive two doses of HRV or placebo:

- Occurrence of any RV GE during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period.

Secondary endpoints:

For the subset of subjects who received two doses of HRV or placebo:

- Occurrence of severe RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of RV GE due to virus types heterologous to vaccine strain during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of any and severe pure RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

- Occurrence of RV GE in which there is at least one other pathogen during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of hospitalization for RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.

For the subset of subjects who received three doses of HRV or placebo:

- Occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 3 until the end of the first efficacy follow-up period.

For the subset of subjects who participated in the second efficacy follow-up period until maximum age 24 months:

- For the subset of subjects who received two doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.
- For the subset of subjects who received two doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the second efficacy follow-up period.
- For the subset of subjects who received three doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.
- For the subset of subjects who received three doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 3 until the end of the second efficacy follow-up period.

Reactogenicity and safety: Recording of solicited symptoms (cough/runny nose, diarrhea, fever, fussiness/irritability, loss of appetite and vomiting) during the 15-day follow-up period (Day 0 to Day 14) after each study vaccination. Recording of unsolicited symptoms during the 43-day follow-up period (Day 0 to Day 42) after each study vaccination and SAEs during the entire study period.

***Secondary endpoints*:**

- For each type of solicited symptoms, occurrence of the symptom within the 15-day solicited follow-up period after any dose of study vaccine (in a subset after Dose 3).
- Occurrence of unsolicited symptoms within 43 days (Day 0 to Day 42) after Dose 1, Dose 2 (in all subjects) and Dose 3 (in a subset) of study vaccination, according to World Health Organization (WHO) classification.
- Occurrence of SAEs throughout the entire study period.

Immunogenicity:

For the subset of subjects planned to receive two doses of HRV or placebo:

Measurement of serum concentration of anti-rotavirus IgA antibodies before Dose 1 (all subjects), two months after Dose 1 (in a subset of subjects), two months after Dose 2 (in a subset of subjects) and at the end of the first efficacy follow-up period (all subjects).

Detection of RV in stool samples (shedding) collected on the day of Dose 1 and Dose 2 and on Day 7±1 after Dose 1 and Dose 2 in the stool analysis subset.

Measurement of serum concentration of antibodies to routine vaccinations (DTPw-HB+Hib and OPV) two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period in a subset of subjects.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

For the subset of subjects who received three doses of HRV or placebo:
Measurement of serum concentration of anti-rotavirus IgA antibodies at Visit 1, two months after Dose 2 and two months after Dose 3 in all subjects from this subset.
Detection of RV (shedding) in stool samples collected on the day of Dose 3 and on Day 7±1 after Dose 3 from all subjects from this subset.
Measurement of serum concentration of antibodies to routine vaccinations (DTPw-HB+Hib and OPV) two months after Dose 2 and two months after Dose 3 of HRV vaccine or placebo in all subjects from this subset.

***Secondary endpoints*:**
For the subset of subjects planned to receive two doses of HRV or placebo:

- Serum rotavirus IgA antibody titers at Visit 1 and the end of the first efficacy follow-up period in all subjects and at Visits 2 and 3 in a subset of subjects.
- Proportion of subjects with vaccine take at Visits 2 and 3 in the stool analysis subset.
- Vaccine take and Geometric Mean Concentration (GMCs) of RV IgA ELISA will be calculated in a subset for breast-fed infants compared with formula fed infants for the following 3 categories: 1) whether the infant received no food 1 hour prior to and 30 minutes after Dose 1 or Dose 2 (as reported by the mother); 2) whether the infant received food 1 hour prior to Dose 1 or Dose 2 (as reported by the mother); and 3) whether the infant received food within 30 minutes after Dose 1 or Dose 2.
- Viral shedding in the vaccine groups in the stool analysis subset.

Two months after Dose 2 (at Visit 3) and at the end of the first efficacy follow-up period in a subset of subjects:

- GMC/Ts for anti-PRP, anti-diphtheria, anti-tetanus, anti-BPT, anti-poliovirus types 1, 2 and 3, and anti-HBs antibodies.
- Seroprotection status:
  - anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml.
  - anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml.
  - anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml.
  - anti-HBs antibody concentrations ≥ 10 mIU/ml.
  - anti-poliovirus type 1 antibody titers ≥ 8.
  - anti-poliovirus type 2 antibody titers ≥ 8.
  - anti-poliovirus type 3 antibody titers ≥ 8.
- Seropositivity status:
  - anti-BPT antibody concentrations ≥ 15 EL.U/ml.

For the subset of subjects who received three doses of HRV or placebo:

- Serum anti-rotavirus IgA antibody concentrations at Visits 1, 3 and 4.
- GMC/Ts for anti-PRP, anti-diphtheria, anti-tetanus, anti-BPT, anti-poliovirus types 1, 2 and 3, and anti-HBs antibodies two months after Dose 3.
- Seroprotection status two months after Dose 3:
  - anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml.
  - anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml.
  - anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml.
  - anti-HBs antibody concentrations ≥ 10 mIU/ml.
  - anti-poliovirus type 1 antibody titers ≥ 8.
  - anti-poliovirus type 2 antibody titers ≥ 8.
  - anti-poliovirus type 3 antibody titers ≥ 8.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

- Seropositivity status two months after Dose 3:
  - anti-BPT antibody concentrations ≥ 15 EL.U/ml
- Viral shedding in the vaccine groups on the day of and on Day 7 after Dose 3.

Statistical methods:

Efficacy:

Primary efficacy analysis for the subset planned to receive two doses of HRV or placebo was performed on the According to Protocol (ATP) cohort.

The duration of the efficacy follow-up period was summarized by group. The percentages of subjects with RV GE (overall, by RV type and by country) of any and severe intensity from 2 weeks after Dose 2 until the end of the first efficacy follow-up period were calculated with their 95% Confidence Interval (CI). The percentages of subjects hospitalized due to RV GE from 2 weeks after Dose 2 until the end of the first efficacy follow-up period were also calculated with their 95% CI. Two-sided Fisher's exact test (significance level of $\alpha = 0.05$) was used to compare these percentages between group.

The efficacy rate (overall, by RV type and by country) of the pooled HRV vaccine groups and each HRV vaccine group relative to the placebo was calculated with its 95% CI against RV GE (any and severe intensity) occurring from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The efficacy rate with its 95% CI was also calculated against hospitalization due to RV GE occurring from 2 weeks after Dose 2 until the end of the first efficacy follow-up period.

Safety and reactogenicity:

Primary analysis of safety and reactogenicity was performed on the total vaccinated cohort. The percentages of doses and of subjects with any symptom (solicited or unsolicited), with specific solicited symptoms reported during the 15-day follow-up period and with unsolicited symptoms classified by WHO Preferred Term reported during the 43-day follow-up period were tabulated with their exact 95% CI. The same calculations were done for symptoms rated as grade "2 or 3" (only for solicited symptoms), those rated as grade "3" in intensity and for those assessed as related to vaccination. Pair-wise differences among the three HRV vaccine groups and between the pooled HRV vaccine group and the placebo group were explored using the two-sided Fisher's exact test for the reactogenicity endpoints, only for the subset of subjects planned to receive two doses of HRV vaccine or placebo. SAEs and discontinuations due to SAEs or non-serious adverse events (AEs) were described.

Immunogenicity:

Primary immunogenicity analysis for the subset planned to receive two doses of HRV or placebo was performed on the ATP cohort. Geometric Mean Concentration/Titer (GMC/T) and seroconversion/seroprotection/seropositivity rates were calculated with their 95% CI for each antibody measured at each blood sampling time point. The percentage of subjects with presence of RV in stool samples collected at Day 0 and Day 7 of each study vaccination was calculated for the stool analysis subset. The proportion of subjects in the stool analysis subset with vaccine take after each dose of HRV vaccine, and after combined doses 1 and 2 were tabulated with their exact 95% CI. Asymptotic standardized two-sided 95% CIs were calculated for difference in vaccine take on combined doses at Visit 3 between each HRV vaccine group and the placebo group.

Differences between each HRV vaccine group and placebo and between the pooled HRV vaccine group and the placebo group with respect to immune response to concomitant vaccination at two months after Dose 2 of HRV vaccine or placebo and at the end of first efficacy follow up period were explored.

Results for the subset planned to receive two doses of HRV vaccine or placebo:

444563/006 Synopsis page 7 of 12

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Demographic results: The mean age of the total vaccinated cohort at the time of the first study vaccine dose was 8.3 weeks (range 6–12 weeks). The demographic profile of the four groups was similar with respect to mean age, mean height and mean weight at the time of Dose 1 of HRV vaccine or placebo and race distribution. Slight differences in gender distribution were observed.

Efficacy results:
The first efficacy follow-up period started from two weeks after Dose 2 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age).
Primary endpoint: A statistically significant decrease in the percentage of subjects reporting any RV GE during the first efficacy follow-up period was detected in the pooled HRV vaccine group and in each HRV vaccine group as compared to the placebo group ($p < 0.05$, two-sided Fisher's exact test).
The efficacy of the vaccine against any RV GE during the first efficacy follow-up period (ATP cohort for efficacy analysis) was as follows:

Group	N	Rate			Vaccine Efficacy			p-value
		%	95% CI		%	95% CI		
			LL	UL		LL	UL	
HRV$10^{4.7}$ ffu	468	4.5	2.8	6.8	58.4	29.4	76.3	<0.001
HRV $10^{5.2}$ ffu	460	4.8	3.0	7.2	55.7	25.3	74.5	<0.001
HRV $10^{5.8}$ ffu	464	3.2	1.8	5.3	70.0	45.7	84.4	<0.001
Pooled HRV	1392	4.2	3.2	5.4	61.4	42.3	74.1	<0.001
Placebo	454	10.8	8.1	14.0	-	-	-	-

N = number of subjects included in each group; 95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Rate = percentage of subjects reporting at least one RV GE episode in each group
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Secondary endpoints (ATP cohort for efficacy analysis):
- During the first efficacy follow-up period, a statistically significant decrease ($p < 0.05$, two-sided Fisher's exact test) in the percentage of infants with severe RV GE and hospitalizations due to RV GE was detected in pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group.
- A statistically significant decrease (p-value < 0.05, two-sided Fisher's exact test) in the percentage of infants with any/severe RV GE caused by G1 type was detected in pooled HRV vaccine group as compared to the placebo group.
- A statistically significant decrease (p-value < 0.05, two-sided Fisher's exact test) in the percentage of infants with any/severe RV GE caused by non-G1 types (either G2, G3, G4 or G9 type) was detected in pooled HRV vaccine groups as compared to the placebo group indicating cross-protection with GSK Biologicals' HRV vaccine.
- Efficacy estimates against pure and mixed RV GE were not calculated since concurrent pathogens were not identified in the majority of RV GE episodes.

Reactogenicity and safety results:
- Incidences of symptoms (solicited or unsolicited) reported within 15 days after vaccination, including those rated as grade "3" and those assessed as related, were similar between the groups.
- Incidences of solicited symptoms, including those rated as grade "2 or 3", those rated as grade "3" and those assessed as related to vaccination, reported within 15 days after vaccination were similar between the groups. There was no increase in reactogenicity from Dose 1 to Dose 2 of HRV vaccine or placebo or with increasing viral concentration.
- Percentages of subjects reporting solicited symptoms during the 15-day follow-up period after any dose of HRV vaccine or placebo (total vaccinated cohort for safety analysis) in subset planned to receive two doses of HRV vaccine or placebo were as follows:

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

		HRV $10^{4.7}$ ffu N = 538			HRV $10^{5.2}$ ffu N = 540			HRV $10^{5.8}$ ffu N = 540			Placebo N = 537		
Symptom		**%**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**
Cough/ runny nose	Total	78.1	74.3	81.5	77.8	74.0	81.2	78.3	74.6	81.7	81.4	77.8	84.6
	Grade 3	16.4	13.3	19.8	16.9	13.8	20.3	17.0	14.0	20.5	13.2	10.5	16.4
	Related	29.2	25.4	33.2	31.1	27.2	35.2	30.4	26.5	34.4	30.2	26.3	34.2
Diarrhea	Total	12.6	10.0	15.7	11.3	8.8	14.3	14.3	11.4	17.5	15.8	12.8	19.2
	Grade 3	3.0	1.7	4.8	4.3	2.7	6.3	4.3	2.7	6.3	4.3	2.7	6.4
	Related	6.5	4.6	8.9	7.6	5.5	10.2	8.3	6.1	11.0	7.6	5.5	10.2
Irritability/ fussiness	Total	78.4	74.7	81.8	80.7	77.2	84.0	81.7	78.1	84.8	82.7	79.2	85.8
	Grade 3	18.0	14.9	21.5	18.0	14.8	21.5	17.6	14.5	21.1	20.3	17.0	24.0
	Related	47.2	42.9	51.5	46.7	42.4	51.0	49.4	45.1	53.7	48.0	43.7	52.4
Loss of appetite	Total	44.6	40.4	48.9	45.6	41.3	49.9	44.6	40.4	48.9	46.9	42.6	51.2
	Grade 3	3.3	2.0	5.2	3.9	2.4	5.9	2.8	1.6	4.5	3.7	2.3	5.7
	Related	20.3	16.9	23.9	20.0	16.7	23.6	19.3	16.0	22.8	22.0	18.5	25.7
Fever	Total	76.2	72.4	79.7	78.1	74.4	81.6	75.2	71.3	78.8	79.1	75.5	82.5
	Grade 3	2.8	1.6	4.6	3.7	2.3	5.7	3.9	2.4	5.9	3.9	2.4	5.9
	Related	43.9	39.6	48.2	41.3	37.1	45.6	41.5	37.3	45.8	41.7	37.5	46.0
Vomiting	Total	22.7	19.2	26.5	27.4	23.7	31.4	24.6	21.1	28.5	24.0	20.5	27.9
	Grade 3	4.5	2.9	6.6	8.1	6.0	10.8	7.2	5.2	9.7	5.0	3.3	7.2
	Related	12.6	10.0	15.7	13.0	10.2	16.1	10.4	7.9	13.3	13.0	10.3	16.2

N = total number of subjects having received at least one dose of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI: exact 95% Confidence Interval, LL = Lower Limit, UL = Upper Limit

- The incidences of the unsolicited symptoms including those rated as grade "3" in intensity or assessed as related to vaccination were similar between the groups.
- Six subjects planned to receive two doses of HRV vaccine or placebo dropped out due to non-serious AEs. Of these, one subject had a vaccination-related AE (grade 2 allergic reaction starting on the day of Dose 1 of study vaccine and concomitant DTPw-HB+Hib vaccine).
- Among the subjects planned to receive two doses of HRV vaccine or placebo, 220 subjects (52 in the $10^{4.7}$ ffu HRV vaccine group, 55 in the $10^{5.2}$ ffu HRV vaccine group, 49 in the $10^{5.8}$ ffu HRV vaccine group and 64 in the placebo group) reported at least one SAE until the end of the first efficacy follow-up period
- All SAEs reported until the end of the first efficacy follow-up period among the subjects planned to receive two doses of HRV vaccine or placebo were assessed as not related to study vaccination (HRV vaccine or placebo) by the respective investigators.
- Three subjects from the subset planned to receive two doses of HRV vaccine or placebo died due to unrelated SAEs during the course of the study.
- One SAE in the subset planned to receive two doses of study vaccine (bronchitis in the $10^{4.7}$ ffu HRV vaccine group) was assessed as possibly related to concomitantly administered routine vaccination (DTPw-HB+Hib) by the investigator.
- One case of intussusception (IS), assessed as not related to vaccination by the investigator, was reported in the subset planned to receive two doses of HRV vaccine or placebo. IS occurred in a 10-month old boy from Mexico, approximately 6 months after the 2nd dose of $10^{4.7}$ ffu HRV vaccine and concomitantly administered routine DTPw-HB+Hib vaccine.
- One SAE in the subset receiving three doses of study vaccine (pneumonia in the placebo group) was assessed as possibly related to the study vaccination by the investigator.

444563/006 Synopsis page 9 of 12

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

Immunogenicity Results: Anti-rotavirus IgA antibody seroconversion rates, GMCs and vaccine take in a subset of subjects two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity analysis) were as follows:

Group	Seroconversion rate at PII(M4)				GMC (U/ml) at PII(M4)				Vaccine take at PII(M4) on combined Doses 1 and 2			
			95% CI				95% CI				95% CI	
	N	%	L.L	U.L	N	Value	L.L	U.L	N	%	L.L	U.L
HRV $10^{4.7}$	142	60.6	52.0	68.7	142	54.0	40.9	71.2	107	64.5	54.6	73.5
HRV $10^{5.2}$	125	62.4	53.3	70.9	125	52.1	39.7	68.3	109	72.5	63.1	80.6
HRV $10^{5.8}$	124	65.3	56.3	73.6	124	70.7	51.9	96.3	106	75.5	66.2	83.3
Placebo	132	5.3	2.2	10.6	132	<20.0	-	-	99	4.0	1.1	10.0

N = number of subjects with available results
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
95% CI: 95% Confidence Interval, LL = Lower Limit, UL = Upper Limit
Seroconversion rate = % with anti-rotavirus IgA antibody concentration ≥ 20 U/ml in subjects initially (i.e. prior to the first dose) negative for RV
Antibody concentration below the cut-off were given an arbitrary value of half the cut-off for GMC calculation
Vaccine take was measured only in the stool analysis subset

The percentages of subjects with RV shedding at Day 7 after Dose 1 ranged from 35.2% to 44.1% between the HRV vaccine groups. There was no shedding on the day of Dose 2 (approximately 2 months after Dose 1), except in one subject in $10^{5.8}$ ffu HRV vaccine group. The percentages of subjects with RV shedding at Day 7 after Dose 2 ranged from 11.5% to 21.3% between the HRV vaccine groups.

Antibody responses to all routine vaccine antigens (D, T, BPT, HBs, PRP, and poliovirus types 1, 2 and 3) at two months after Dose 2 of HRV vaccine or placebo in the three HRV vaccine groups were similar to those of the placebo (control) indicating that there appeared to be no impact of HRV vaccine on immunogenicity of OPV and concomitantly administered DTPw-HB+Hib vaccine, except for anti-diphtheria antibodies. There was a trend towards lower anti-diphtheria antibody seroprotection rates in the $10^{4.7}$ ffu and $10^{5.2}$ ffu HRV vaccine groups as compared to the placebo group at two months after Dose 2 of HRV vaccine or placebo. Persistence data for antibodies to all routine vaccine antigens at end of the first efficacy follow-up period in the three HRV vaccine groups were similar to those of the placebo (control) indicating that there was no apparent effect of the HRV vaccine on the immunogenicity of routine vaccines after completion of the three-dose primary vaccination course of routine vaccines.

Conclusions:
Study rota-006 demonstrated that two doses of GSK Biologicals' HRV vaccine were well tolerated, immunogenic and efficacious in protecting susceptible infants until approximately one year of age against RV GE in the Latin American setting where G1 and non-G1 RV serotypes were circulating. The highest viral concentration ($10^{5.8}$ ffu) evaluated showed higher immunogenicity and protection without increased reactogenicity.

Efficacy

- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups and each viral concentration) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of any RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The observed vaccine efficacy ranged between 55.7% to 70%. Thus, the primary objective of the study was met.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**

- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups and each viral concentration) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of severe RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The observed vaccine efficacy ranged between 65.8% to 85.6%.
- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of hospitalization due to RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The observed vaccine efficacy in pooled HRV vaccine groups was 79%.
- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of any and severe RV GE caused by G1 and non-G1 serotypes relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. Proof of concept that GSK Biologicals' monovalent G1[P8] HRV vaccine exhibits clinical protection against homotypic and heterotypic strains was thus demonstrated in the Latin American setting where G1 and non-G1 serotypes were circulating.
- The highest viral concentration of GSK Biologicals' HRV vaccine evaluated, $10^{5.8}$ ffu, consistently performed better in terms of homotypic and heterotypic protection against any and severe RV GE.

Safety/Reactogenicity

- The safety and reactogenicity profile of two doses of each viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations was similar to that of the placebo in terms of the incidences of solicited/unsolicited symptoms and SAEs reported after vaccination. There was no increase in reactogenicity with the use of higher viral concentration and from Dose 1 to Dose 2.
- Even the highest viral concentration used, HRV vaccine at $10^{5.8}$ ffu, did not result in increased reactogenicity as compared to placebo, confirming the mild reactogenicity profile of GSK Biologicals' attenuated HRV vaccine.

Immunogenicity

- Vaccine take rates ranged from 48.6% to 57.4% at two months after the first dose of GSK Biologicals' HRV vaccine containing $10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu. Vaccine take rates ranged from 62.6% to 69.1% at two months after the second dose.
- Persistence in terms of serum anti-rotavirus IgA antibodies at the end of the first efficacy follow-up period (approximately 8 months after the second dose) was similar for the three viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine.
- RV shedding was observed predominantly after Dose 1 of GSK Biologicals' HRV vaccine with little residual shedding two months after Dose 1.
- There was a trend towards higher immunogenicity in terms of IgA seroconversion rates, GMCs and vaccine take in the $10^{5.8}$ ffu HRV vaccine group at two months after Dose 2.
- The effect of unrestricted feeding on the immunogenicity of the HRV vaccine was evaluated and indicated that none of the pre-defined feeding criteria had a significant effect.
- GSK Biologicals' HRV vaccine did not appear to impact on immunogenicity of routine vaccines, DTPw-HB and Hib (given concomitantly) or OPV vaccine.

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium **Name of Finished Product:** HRV vaccine **Name of active substance:** RIX4414	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	**(for national authority only)**
Exploratory evaluation of three doses of HRV vaccine in a subset of subjects • Within the limits of the small sample size, three doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups and each viral concentration) given concomitantly to healthy infants with routine vaccinations appeared to decrease the incidence of any and severe RV GE relative to the placebo during the period starting from 2 weeks after Dose 3 until the end of the first efficacy follow-up period. • The safety and reactogenicity profile of the three doses of each viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations was similar to that of the placebo in terms of the incidences of solicited/unsolicited symptoms and SAEs reported after vaccination. • Anti-rotavirus IgA antibody responses in terms of seropositivity and GMCs were similar for the three viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) at two months after the second dose and at two months after the third dose of GSK Biologicals' HRV vaccine. There was a trend towards higher immunogenicity in the $10^{5.8}$ ffu HRV vaccine group. • RV shedding observed after the third dose of GSK Biologicals' HRV vaccine was similar for the three viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu). • GSK Biologicals' HRV vaccine did not appear to impact on immunogenicity of routine vaccines, DTPw-HB and Hib (given concomitantly) or OPV vaccine.		
Date of report: November 14, 2003		
444563/006 Synopsis page 12 of 12		

CONTENTS: TEXT

Synopsis of Final Report for Clinical Trial 444563/006 (rota-006) ***2***

1 Introduction/Rationale ***29***

2 Study Objectives ***30***

2.1 Primary objective **30**

2.2 Secondary objectives **31**

3 Methodology ***33***

3.1 Study design **33**

3.2 Investigators and trial centres **35**

3.3 Ethics **36**
3.3.1 Protocol amendments/modifications 37

3.4 Selection of study population **39**
3.4.1 Inclusion criteria 39
3.4.2 Exclusion criteria 39
3.4.3 Elimination criteria during the study up to Visit 3 (up to Visit 4 for the subset of subjects receiving three doses of study vaccine or placebo) 40
3.4.4 Elimination criteria during the study from Visit 3 (from Visit 4 for the subset of subjects receiving three doses of study vaccine or placebo) until study end 41
3.4.5 Contraindications to vaccination 41

3.5 Study vaccines and administration **42**
3.5.1 GSK Biologicals' HRV vaccine 43
3.5.2 GSK Biologicals' placebo for HRV vaccine 43
3.5.3 GSK Biologicals' calcium carbonate buffer used as diluent 43
3.5.4 Dosage and administration 43

3.6 Routine vaccines and administration **44**
3.6.1 GSK Biologicals' DTPw-HB+Hib vaccine 44
3.6.2 GSK Biologicals' OPV (Polio Sabin) vaccine 45
3.6.3 Dosage and administration 45

3.7 Treatment allocation and randomization **45**
3.7.1 Randomization of supplies 45
3.7.2 Randomization of subjects 46
3.7.3 Subset definition 46

3.8 Blinding **47**

3.9 Study procedures **48**

3.10 Subject completion and drop out **49**

3.11 Assessment of efficacy variables **50**
3.11.1 Diarrheal stool analysis 53

3.12 Assessment of safety variables **53**
3.12.1 Pregnancy 57
3.12.2 Prior and concomitant medication 57

3.13 Assessment of immunogenicity variables **58**
3.13.1 Intervals between study visits 58
3.13.2 Laboratory assays and timepoints 59
3.13.2.1 Stool analysis 59

3.13.2.2 Serum analysis ... 60

3.14 Data quality assurance ... 61

3.15 Statistical methods ... 62
3.15.1 Primary endpoint ... 62
3.15.2 Secondary endpoints ... 63
3.15.3 Determination of sample size ... 65
3.15.4 Study cohorts/data sets analyzed ... 68
3.15.5 Analysis of demographics ... 70
3.15.5.1 For the subset planned to receive two doses of HRV vaccine or placebo ... 70
3.15.5.2 For the subset receiving three doses of HRV vaccine or placebo ... 70
3.15.6 Analysis of efficacy ... 71
3.15.6.1 Efficacy during first efficacy follow-up period for the subset planned to receive two doses of HRV vaccine or placebo ... 71
3.15.6.2 Exploratory efficacy during the first efficacy follow-up period for the subset receiving three doses of HRV vaccine or placebo ... 73
3.15.7 Analysis of safety ... 73
3.15.7.1 Reactogenicity of two doses of HRV vaccine and placebo ... 73
3.15.7.2 Reactogenicity of HRV vaccine and placebo in the subset receiving three doses of HRV vaccine or placebo ... 75
3.15.8 Analysis of immunogenicity ... 76
3.15.8.1 Immunogenicity of the HRV vaccine for the subset planned to receive two doses of HRV vaccine or placebo ... 76
3.15.8.2 Immunogenicity of routine DTPw-HBV+Hib and OPV vaccines for the subset receiving two doses of HRV vaccine or placebo ... 79
3.15.8.3 Immunogenicity analysis for the subset receiving three doses of HRV vaccine or placebo ... 80

3.16 Interim analyses ... 81

3.17 Annex analyses ... 82

3.18 Changes in conduct of the study/planned analyses ... 82

4 Study population planned to receive two doses of HRV vaccine or placebo ... 83

4.1 Study dates ... 83

4.2 Subject eligibility and attrition from study ... 83
4.2.1 Number and distribution of subjects ... 83
4.2.2 Study completion and drop out ... 84
4.2.3 Eligibility for analysis ... 86
4.2.4 Compliance with protocol specified procedures ... 88

4.3 Demographic characteristics ... 90
4.3.1 Total vaccinated cohort ... 90
4.3.2 Subjects included in the ATP cohort for efficacy analysis ... 90
4.3.3 Subjects included in the ATP cohort for immunogenicity analysis ... 91

5 Analysis of efficacy in subjects planned to receive two doses of HRV vaccine or placebo ... 92

5.1 Data sets analyzed ... 92

5.2 ATP analysis ... 92
5.2.1 Characterization of GE episodes reported during the first efficacy follow-up period ... 92
5.2.2 Vaccine efficacy against RV GE during the first efficacy follow-up period ... 94
5.2.3 Vaccine efficacy against hospitalization due to RV GE during the first efficacy follow-up period ... 98
5.2.4 Total vaccinated cohort for efficacy analysis ... 99

5.2.4.1 Vaccine efficacy against RV GE occurring from Dose 1 onwards 99

6 Analysis of safety in subjects planned to receive two doses of HRV vaccine or placebo 101

6.1 Data sets analyzed 101

6.2 Total vaccinated cohort for safety analysis 102
6.2.1 Overall incidence of symptoms 102
6.2.2 Solicited signs and symptoms 103
6.2.3 Unsolicited symptoms 111
6.2.4 Concomitant medications 115
6.2.5 Reactogenicity analysis by country 117
6.2.6 Serious adverse events 117
6.2.6.1 SAEs assessed as possibly related to the concomitantly administered routine vaccination 118
6.2.6.2 SAEs with fatal outcome 118
6.2.6.3 IS 119
6.2.6.4 SAEs ongoing at the data lock point for analysis 121

6.3 ATP cohort for safety analysis 121

7 Analysis of immunogenicity in subjects planned to receive two doses of HRV vaccine or placebo 121

7.1 Data sets analyzed 121

7.2 ATP cohort for immunogenicity analysis 121
7.2.1 Immunogenicity of the HRV vaccine 121
7.2.2 Immunogenicity of the HRV vaccine in the stool analysis subset 123
7.2.3 Impact of feeding on immunogenicity of HRV vaccine 129
7.2.4 Immunogenicity analysis by country 129
7.2.5 Immunogenicity of routine vaccinations (DTPw-HB+Hib and OPV) 129

7.3 Total vaccinated cohort for immunogenicity analysis 137

8 Exploratory evaluation of three doses of HRV vaccine or placebo 137

8.1 Study population receiving three doses of HRV vaccine or placebo 137
8.1.1 Study dates 137

8.2 Subject eligibility and attrition from study 138
8.2.1 Number and distribution of subjects 138
8.2.2 Study completion and drop out 138
8.2.3 Eligibility for analysis 138
8.2.4 Compliance with protocol specified procedures 138

8.3 Demographic characteristics of the total vaccinated cohort 139

8.4 Exploratory analysis of efficacy 140
8.4.1 Data sets analyzed 140
8.4.2 Total vaccinated cohort for efficacy analysis 140
8.4.2.1 Characterization of GE episodes reported during the first efficacy follow-up period. 140

8.5 Analysis of safety 141
8.5.1 Data sets analyzed 141
8.5.2 Total vaccinated cohort for safety analysis 142
8.5.2.1 Overall incidence of symptoms 142
8.5.2.2 Solicited signs and symptoms 143
8.5.2.3 Unsolicited symptoms 150

8.5.2.4 Concomitant medications 152
8.5.3 Serious adverse events 154

8.6 Analysis of immunogenicity 155
8.6.1 Data sets analyzed 155
8.6.2 Total vaccinated cohort for immunogenicity analysis 155
8.6.2.1 Immunogenicity of GSK Biologicals' HRV vaccine 155
8.6.2.2 Immunogenicity of routine vaccinations (DTPw-HB+Hib and OPV) 158

9 Discussion 164

10 Overall Conclusions 168

11 References 171

CONTENTS: REPORT TABLES

TABLE 1: THE GSK ASSIGNED CENTRE NUMBERS, INVESTIGATIONAL SITES AND INVESTIGATORS.. 36
TABLE 2: ETHICS COMMITTEES FOR EACH CENTRE 37
TABLE 3: OUTLINE OF STUDY PROCEDURES 48
TABLE 4: THE 20-POINT SCORING SYSTEM USED TO ASSESS THE SEVERITY OF EACH DIARRHEA EPISODE 52
TABLE 5: INTENSITY SCALES FOR SOLICITED SYMPTOMS 54
TABLE 6: INTERVALS BETWEEN STUDY VISITS* FOR SUBJECTS PLANNED TO RECEIVE TWO DOSES OF HRV VACCINE OR PLACEBO 58
TABLE 7: INTERVALS BETWEEN STUDY VISITS* FOR SUBJECTS RECEIVING THREE DOSES OF HRV VACCINE OR PLACEBO 59
TABLE 8: SEROLOGICAL ASSAYS FOR ANTIBODIES TO CONCOMITANTLY ADMINISTERED ROUTINE VACCINATIONS 61
TABLE 9: POWER TO GET AN EXACT 95% CI FOR THE VACCINE EFFICACY FOR A VACCINE GROUP ABOVE A SPECIFIC CUT-OFF (N = 460 SUBJECTS BY GROUP, POWER BASED ON 1.000 SIMULATIONS USING PROC STATXACT) (REFER TO APPENDIX B FOR MATHEMATICAL DETAILS) 66
TABLE 10: THE NUMBER OF SUBJECTS ENROLLED AT EACH STUDY CENTRE BY GROUP (TOTAL VACCINATED COHORT) 84
TABLE 11: COUNTS OF SUBJECTS ENROLLED, COMPLETED, DROPPED OUT AND REASON FOR DROP OUT UNTIL THE END OF THE FIRST EFFICACY FOLLOW-UP PERIOD (TOTAL VACCINATED COHORT). 84
TABLE 12: NUMBER OF SUBJECTS ENROLLED INTO THE STUDY AS WELL AS THE NUMBER OF SUBJECTS EXCLUDED FROM ATP ANALYSES WITH REASONS FOR EXCLUSION 86
TABLE 13: SUMMARY OF DEMOGRAPHIC CHARACTERISTICS (ATP COHORT FOR EFFICACY ANALYSIS) 91
TABLE 14: NUMBER OF GE EPISODES AND RV GE EPISODES REPORTED DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY SEVERITY (ATP COHORT FOR EFFICACY ANALYSIS) 93
TABLE 15: PERCENTAGE OF SUBJECTS WITH RV GE EPISODES REPORTED DURING THE FIRST EFFICACY FOLLOW-UP PERIOD, BY RV G TYPE (ATP COHORT FOR EFFICACY ANALYSIS) 94
TABLE 16: PERCENTAGE OF SUBJECTS REPORTING ANY RV GE AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (ATP COHORT FOR EFFICACY ANALYSIS) 96

TABLE 17: PERCENTAGE OF SUBJECTS REPORTING SEVERE RV GE AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (ATP COHORT FOR EFFICACY ANALYSIS) . 96
TABLE 18: PERCENTAGE OF SUBJECTS HOSPITALIZED DUE TO RV GE AND EFFICACY OF THE VACCINE DURING THE FIRST EFFICACY FOLLOW-UP PERIOD (ATP COHORT FOR EFFICACY ANALYSIS) . 99
TABLE 19: NUMBER AND PERCENTAGE OF SUBJECTS WHO RECEIVED VACCINE DOSE(S) (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 102
TABLE 20: PERCENTAGE OF DOSES AND OF SUBJECTS REPORTING SYMPTOMS (SOLICITED OR UNSOLICITED) DURING THE 15-DAY SOLICITED FOLLOW-UP PERIOD (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 103
TABLE 21: PERCENTAGE OF SUBJECTS WITH EACH SOLICITED SYMPTOM INCLUDING THOSE GRADED "2 OR 3", GRADED "3" IN INTENSITY AND THOSE CONSIDERED TO BE RELATED TO VACCINATION, DURING THE 15-DAY FOLLOW-UP PERIOD **AFTER DOSE 1** OF HRV VACCINE OR PLACEBO (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 105
TABLE 22: PERCENTAGE OF SUBJECTS WITH EACH SOLICITED SYMPTOM INCLUDING THOSE GRADED "2 OR 3", GRADED "3" IN INTENSITY AND THOSE CONSIDERED TO BE RELATED TO VACCINATION, DURING THE 15-DAY FOLLOW-UP PERIOD **AFTER DOSE 2** OF HRV VACCINE OR PLACEBO (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 107
TABLE 23: STATISTICAL COMPARISONS BETWEEN GROUPS FOR PERCENTAGE OF SUBJECTS REPORTING EACH SOLICITED SYMPTOM AFTER ANY DOSE OF HRV VACCINE OR PLACEBO (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 110
TABLE 24: THE PERCENTAGE OF SUBJECTS WITH UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS ASSESSED AS **RELATED** TO VACCINATION, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 111
TABLE 25: THE PERCENTAGE OF SUBJECTS WITH **GRADE "3"** UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 113
TABLE 26: PERCENTAGE OF DOSES WITH AT LEAST ONE CONCOMITANT MEDICATION ADMINISTERED FROM DAY 0 TO DAY 14 AFTER VACCINATION, BY TYPE (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 116
TABLE 27: ANTI-ROTAVIRUS IGA ANTIBODY GMCS AND SEROPOSITIVITY RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 122
TABLE 28: ANTI-ROTAVIRUS IGA ANTIBODY SEROCONVERSION RATES ON COMBINED DOSES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 123
TABLE 29: ANTI-ROTAVIRUS IGA ANTIBODY GMCS CALCULATED ON SUBJECTS SEROPOSITIVE FOR ANTI-ROTAVIRUS IGA ANTIBODIES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 123
TABLE 30: ANTI-ROTAVIRUS IGA ANTIBODY GMCS AND SEROPOSITIVITY RATE (STOOL ANALYSIS SUBSET, ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 124
TABLE 31: NUMBER OF SUBJECTS WITH VACCINE VIRUS IN STOOL SAMPLES COLLECTED AT PRE-DETERMINED TIMEPOINTS (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 126
TABLE 32: PERCENTAGE OF SUBJECTS WITH VACCINE VIRUS IN STOOL SAMPLES COLLECTED AT PRE-DETERMINED TIME POINTS, ON COMBINED TIME POINTS (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 127

TABLE 33: PERCENTAGE OF SUBJECTS WITH VACCINE TAKE AFTER EACH DOSE OF HRV VACCINE OR PLACEBO (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 127
TABLE 34: PERCENTAGE OF SUBJECTS WITH VACCINE TAKE AFTER COMBINED DOSES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 128
TABLE 35: DIFFERENCE IN PERCENTAGE OF SUBJECTS WITH VACCINE TAKE ON COMBINED DOSES 1 AND 2 AT TWO MONTHS AFTER DOSE 2 OF HRV VACCINE OR PLACEBO (AT VISIT 3) BETWEEN EACH HRV VACCINE AND PLACEBO GROUPS (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) ... 129
TABLE 36: ANTI-DIPHTHERIA ANTIBODY GMCS AND SEROPROTECTION RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 131
TABLE 37: ANTI-TETANUS ANTIBODY GMCS AND SEROPROTECTION RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 132
TABLE 38: ANTI-BPT ANTIBODY GMCS AND SEROPOSITIVITY RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 133
TABLE 39: ANTI-HBS ANTIBODY GMCS AND SEROPROTECTION RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 134
TABLE 40: ANTI-PRP ANTIBODY GMCS AND SEROPROTECTION RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 135
TABLE 41: ANTI-POLIOVIRUS TYPES 1, 2 AND 3 ANTIBODY GMTS AND SEROPROTECTION RATES (ATP COHORT FOR IMMUNOGENICITY ANALYSIS) 136
TABLE 42: PERCENTAGE OF SUBJECTS REPORTING ANY RV GE FROM 2 WEEKS AFTER DOSE 3 OF HRV VACCINE OR PLACEBO UNTIL END OF THE FIRST EFFICACY FOLLOW-UP PERIOD (TOTAL VACCINATED COHORT FOR EFFICACY ANALYSIS) 141
TABLE 43: PERCENTAGE OF SUBJECTS REPORTING SEVERE RV GE FROM 2 WEEKS AFTER DOSE 3 OF HRV VACCINE OR PLACEBO UNTIL END OF THE FIRST EFFICACY FOLLOW-UP PERIOD (TOTAL VACCINATED COHORT FOR EFFICACY ANALYSIS) 141
TABLE 44: PERCENTAGE OF DOSES AND OF SUBJECTS REPORTING SYMPTOMS (SOLICITED OR UNSOLICITED) DURING THE 15-DAY SOLICITED FOLLOW-UP PERIOD (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 143
TABLE 45: PERCENTAGE OF SUBJECTS WITH EACH SOLICITED SYMPTOM INCLUDING THOSE GRADED "2 OR 3", THOSE GRADED "3" IN INTENSITY AND THOSE CONSIDERED TO BE RELATED TO VACCINATION, DURING THE 15-DAY FOLLOW-UP PERIOD AFTER **DOSE 1** OF HRV VACCINE OR PLACEBO (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 145
TABLE 46: PERCENTAGE OF SUBJECTS WITH EACH SOLICITED SYMPTOM INCLUDING THOSE GRADED "2 OR 3", THOSE GRADED "3" IN INTENSITY AND THOSE CONSIDERED TO BE RELATED TO VACCINATION, DURING THE 15-DAY FOLLOW-UP PERIOD AFTER **DOSE 2** OF HRV VACCINE OR PLACEBO (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 147
TABLE 47: PERCENTAGE OF SUBJECTS WITH EACH SOLICITED SYMPTOM INCLUDING THOSE GRADED "2 OR 3", THOSE GRADED "3" IN INTENSITY AND THOSE CONSIDERED TO BE RELATED TO VACCINATION, DURING THE 15-DAY FOLLOW-UP PERIOD AFTER **DOSE 3** OF HRV VACCINE OR PLACEBO (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 149

TABLE 48: THE PERCENTAGE OF SUBJECTS WITH UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS ASSESSED AS RELATED TO VACCINATION, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 151
TABLE 49: THE PERCENTAGE OF SUBJECTS WITH GRADE 3 UNSOLICITED SYMPTOMS CLASSIFIED BY WHO PREFERRED TERMS, FROM DAY 0 TO DAY 42 AFTER ANY VACCINATION (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS) 152
TABLE 50: PERCENTAGE OF DOSES WITH AT LEAST ONE CONCOMITANT MEDICATION ADMINISTERED FROM DAY 0 TO DAY 14 AFTER VACCINATION, BY TYPE (TOTAL VACCINATED COHORT FOR SAFETY ANALYSIS)..... 153
TABLE 51: ANTI-ROTAVIRUS IGA ANTIBODY GMCS AND SEROPOSITIVITY RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 156
TABLE 52: ANTI-ROTAVIRUS IGA ANTIBODY GMCS CALCULATED ON SUBJECTS SEROPOSITIVE FOR ANTI-ROTAVIRUS IGA ANTIBODIES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 157
TABLE 53: NUMBER OF SUBJECTS WITH VACCINE VIRUS IN STOOL SAMPLES COLLECTED AT PRE-DETERMINED TIMEPOINTS (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS)158
TABLE 54: ANTI-DIPHTHERIA ANTIBODY GMCS AND SEROPROTECTION RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 159
TABLE 55: ANTI-TETANUS ANTIBODY GMCS AND SEROPROTECTION RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 160
TABLE 56: ANTI-BPT ANTIBODY GMCS AND SEROPOSITIVITY RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 160
TABLE 57: ANTI-HBS ANTIBODY GMCS AND SEROPROTECTION RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 161
TABLE 58: ANTI-PRP ANTIBODY GMCS AND SEROPROTECTION RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS) 162
TABLE 59: ANTI-POLIOVIRUS TYPES 1, 2 AND 3 ANTIBODY GMTS AND SEROPROTECTION RATES (TOTAL VACCINATED COHORT FOR IMMUNOGENICITY ANALYSIS)..... 163

CONTENTS: SUPPLEMENTS

Supplements 1–11 : Compliance and demography for subjects planned to receive two doses of HRV vaccine or placebo

Supplements 12–42 : Efficacy for subjects planned to receive two doses of HRV vaccine or placebo

Supplements 43–98 : Reactogenicity and safety for subjects planned to receive two doses of HRV vaccine or placebo

Supplements 99–167 : Immunogenicity for subjects planned to receive two doses of HRV vaccine or placebo

Supplements 168–188 : Exploratory evaluation of three doses of HRV vaccine

APPENDICES

APPENDIX A: CLINTRIAL ELIGIBILITY CODES
APPENDIX B: MATHEMATICAL DETAILS* ABOUT THE COMPUTATION OF THE 95%CI FOR VACCINE EFFICACY
APPENDIX C: LABORATORY ASSAYS

INDIVIDUAL DATA LISTING NOT PROVIDED SINCE SECOND YEAR EFFICACY FOLLOW-UP WAS ONGOING AT DATA LOCK POINT FOR THE ANALYSIS.

APPENDIX: SERIOUS ADVERSE EVENTS
- SERIOUS ADVERSE EVENTS TABLE
- CLINICAL NARRATIVES FOR THE SERIOUS ADVERSE EVENTS

APPENDICES: STUDY INFORMATION
- PROTOCOL
- REPRESENTATIVE SUBJECT INFORMATION SHEET
- RELEVANT PAGES OF CRF (UNIQUE PAGES ONLY)
- ONE PAGE CV (*curriculum vitae)* FOR PRINCIPAL INVESTIGATORS
- PUBLICATIONS REFERENCED IN THE REPORT

List of Abbreviations

AE	Adverse Event
ATP	According to Protocol
BCG	Bacillus Calmette-Guerin
BPT	*Bordetella pertussis*
$CCID_{50}$	median Cell Culture Infective Dose
CI	Confidence Interval
cm	Centimeter
eCRF	electronic Case Report Form
DTPw-HB+Hib	Diphtheria-tetanus-whole-cell pertussis-hepatitis B-*Haemophilus influenzae* type b vaccine
ELISA	Enzyme Linked Immunosorbent Assay
EL.U	ELISA units
EPI	Expanded Program on Immunization
ES	End of season
ffu	Foci forming units
GCP	Good Clinical Practice
GE	Gastroenteritis
GMC/T	Geometric Mean Concentration/Titer
GSK	GlaxoSmithKline
HBs	Hepatitis B surface antigen
HBV	Hepatitis B Vaccine
HRV	Human Rotavirus
HIV	Human Immunodeficiency Virus
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A
IS	Intussusception
IU	International Units
Kg	Kilogram
LCL	Lower Confidence Limit
LF	Limit Floculation
LL	Lower Limit
MedDRA	Medical Dictionary for Regulatory Activities
mcg	Microgram
mg	Milligram
mIU	Milli-International Units
ml	Milliliters
MOH	Ministry of Health
OPV	Oral Polio Vaccine
OU	Opacity Units
PID	Patient Identification Number
PRP	Polyribosyl Ribitol Phosphate
RDE	Remote Data Entry
RIBA	Recombinant ImmunoBlot Assay
RRV-TV	Rhesus-human Reassortant Rotavirus Vaccine TetraValent

RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RV	Rotavirus
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
U	Units
UL	Upper Limit
WHO	World Health Organization
WRC	Worldwide Regulatory Compliance

Glossary of Terms

According to protocol cohort:	Includes all subjects enrolled in the study who met the criteria defined in the protocol for the considered analysis (efficacy, reactogenicity or immunogenicity).
Adverse event:	Any noxious, pathologic or unintended change in anatomical, physiologic and/or laboratory detected changes occurring in any phase of the clinical trial whether associated with vaccination or whether or not considered vaccine related.
Completed:	Subject who completed the final study visit foreseen in the protocol.
Diarrhea:	Three or more looser than normal stools within a day.
Diary card:	Individual card provided by the sponsor for each vaccinee after each vaccine dose designed to document the presence of solicited adverse events as well as any other sign/symptom the vaccinee might experience.
Drop out:	Subject who did not return for the final study visit foreseen in the protocol.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Enrolled:	Participated in the first visit of the study after written informed consent obtained from parents/guardians, determined to be eligible for inclusion in the study based upon strict adherence to inclusion/exclusion criteria.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in analysis.
Independent Data Monitoring Committee	The IDMC was responsible for safety monitoring during the [rotavirus] trials taking into account the

(IDMC)	potential benefits of the vaccine in different parts of the world.
First efficacy follow-up period:	**For subjects planned to receive two doses of HRV vaccine or placebo:** The first efficacy follow-up period started from two weeks after Dose 2 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age). **For subjects who received three doses of HRV vaccine or placebo:** The first efficacy follow-up period started from two weeks after Dose 3 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age).
Gastroenteritis:	Diarrhea.
Mixed rotavirus gastroenteritis:	Gastroenteritis associated with rotavirus and at least one other pathogen: An episode of rotavirus gastroenteritis for which at least one other pathogen was identified in stool sample(s) collected from the start of the gastroenteritis episode to the minimum of the following 2 timepoints either 7 days after the end of the gastroenteritis episode or the day before the next gastroenteritis episode, if subject had several episodes of gastroenteritis.

Pure rotavirus gastroenteritis:	Rotavirus gastroenteritis with no other identified concurrent pathogen infection.
Rotavirus gastroenteritis:	All rotavirus gastroenteritis (pure and mixed rotavirus gastroenteritis).
Rotavirus gastroenteritis caused by the circulating wild-type rotavirus strains:	**For the subset of subjects who received two doses of HRV or placebo:** • From Visits 1 to 3: all gastroenteritis episodes in which rotavirus other than vaccine strain was identified in a stool sample collected during the episode. • From Visit 3 onwards: all gastroenteritis episodes in which rotavirus was identified in a stool sample collected during the episode. **For the subset of subjects who received three doses of HRV or placebo:** • From Visits 1 to 4: all gastroenteritis episodes in which rotavirus other than vaccine strain was identified in a stool sample collected during the episode. • From Visit 4 onwards: all gastroenteritis episodes in which rotavirus was identified in a stool sample collected during the episode.
Rotavirus gastroenteritis for efficacy analysis:	**For the subset of subjects planned to receive two doses of HRV or placebo:** An episode of gastroenteritis (diarrhea) occurring at least two weeks after Dose 2 in which rotavirus other than vaccine strain was identified in a stool sample collected during the episode of gastroenteritis. **For the subset of subjects who received three doses of HRV or placebo:** An episode of gastroenteritis (diarrhea) occurring at least two weeks after Dose 3 in which rotavirus other than vaccine strain was identified in a stool sample collected during the episode of gastroenteritis. Stool samples collected from the start of the gastroenteritis episode to the minimum of the following 2 timepoints either 7 days after the end of the gastroenteritis episode or the day before the next

	gastroenteritis episode, if subject had several episodes of gastroenteritis were considered.
Separate episodes of gastroenteritis:	Two occurrences of gastrointestinal symptoms with 5 or more symptoms-free days between the episodes.
Second efficacy follow-up period:	Second efficacy follow-up took place after visit at the end of the first efficacy follow-up period until a maximum of two years of age. The second efficacy follow-up period ended in June 2003 after the end of the 2003 rotavirus season in Mexico (for subjects from Mexico) and in October 2003 (for subjects from Brazil and Venezuela).
Seroconversion:	Appearance of anti-rotavirus IgA antibody concentration ≥ 20 units (U)/milliliter (ml in subjects initially (i.e. prior to the first dose of HRV vaccine or placebo) negative for rotavirus.
Seronegative:	A subject whose antibody concentration was below the assay cut-off value.
Seropositive:	A subject whose antibody concentration was greater than or equal to the assay cut-off value.
Seroprotected:	A subject whose antibody concentration was greater than or equal to the seroprotective level.
Severe rotavirus gastroenteritis:	An episode of rotavirus gastroenteritis with score ≥ 11 on a 20 point scoring system.
Subject(s)/Vaccinee(s):	Terms used throughout the report to denote the enrolled/vaccinated individual(s).
Symptom sheets:	The specific pages in the individual case report forms onto which the investigator transcribed diary card documentation on solicited symptom(s) reported for the subject.
Total vaccinated cohort:	All subjects with at least one study vaccine administration documented.

Vaccine take: The appearance of serum IgA to rotavirus in post-immunization sera at a concentration ≥ 20 U/ml and/or vaccine virus shedding in any stool sample collected from Visit 1 to Visit 3.

In Study 006, vaccine take was calculated only for the stool analysis subset (subjects who provided blood and stool samples).

Vomiting: One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

1 Introduction/Rationale

An attenuated human rotavirus (HRV) vaccine candidate was developed from the 89-12 HRV strain belonging to the serotype G1P1A and genotype [P8]. Initial development of the 89-12 vaccine at passage 33 has demonstrated its safety, immunogenicity and efficacy in infants ([1], [2]). GlaxoSmithKline (GSK) Biologicals has implemented several process changes to the 89-12 vaccine candidate at passage 33 to develop a lyophilized HRV vaccine containing a cloned 89-12 HRV strain at passage 43, referred to as RIX4414.

Study rota-006 was a randomized, placebo-controlled, double-blind, dose-range study conducted in Brazil, Mexico and Venezuela to assess the efficacy, reactogenicity, safety and immunogenicity of two doses of GSK Biologicals' HRV vaccine at different viral concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ foci forming units (ffu)) in healthy infants (approximately 2 months of age at first dose of HRV vaccine or placebo) following a 0, 2 month schedule. This study also assessed the immunogenicity of routine vaccinations: diphtheria-tetanus-whole-cell pertussis-hepatitis B-*Haemophilus influenzae* type b vaccine (DTPw-HB+Hib vaccine)] given concurrently with HRV vaccine or placebo and Oral Polio Vaccine (OPV) given separately outside a 2-week interval from HRV vaccine/placebo. All subjects were followed for efficacy until approximately one year of age. The efficacy, reactogenicity, safety and immunogenicity results obtained until the end of the first efficacy follow-up period after vaccination are presented in this study report.

Administration of a third dose of the HRV vaccine or its placebo at approximately 6 months of age was explored in a subset of subjects and results of this evaluation are also presented in this study report.

A subset of subjects participated in the second efficacy follow-up period (until maximum age 24 months). A separate annex report will present efficacy and safety data during the second efficacy follow-up period from all subjects (from Brazil, Mexico and Venezuela) who were followed until maximum age 24 months.

A subset of subjects from Mexico participated in study rota-008, an annex protocol titled "To assess the impact of breast milk lactadherin, breast milk rotavirus Immunoglobulin A (IgA) antibodies and maternal IgG antibodies on the immunogenicity of GSK Biologicals' HRV vaccine". The analyses for transplacental anti-rotavirus IgG antibodies and transplacental anti-rotavirus neutralizing antibodies in study rota-008 are available and are presented in the report "The Interference of Transplacental Antibodies on Response to GSK Biologicals' Human Rotavirus Vaccine: Rota-004, Rota-008 and Rota-014". A separate report will present all data obtained in study rota-008.
A subset of subjects from Venezuela participated in a site-specific evaluation of fecal RV IgA immune response and the role of IgA antibodies as marker of protection against RV disease. A separate report will present all data from this evaluation.

A separate report will present all data on characterisation of the immune response of the HRV vaccine (maternal antibodies and neutralizing antibodies) from subsets of subjects enrolled in study rota-006.

2 Study Objectives

Note: Although all study objectives are listed, only analyses of data obtained until the end of the first efficacy follow-up period are presented in this study report.

2.1 Primary objective

For the subset of subjects planned to receive two doses of HRV or placebo:

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine, to demonstrate the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations in preventing any rotavirus (RV) gastroenteritis (GE) during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period.

Refer to the glossary of terms for definition of terms used.

See Section 3.15.1 for delineation of the primary endpoint.

2.2 Secondary objectives

Efficacy

First efficacy follow-up period

For the subset of subjects planned to receive two doses of HRV or placebo:

- For a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine, to assess if two doses of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations can:
  - Prevent severe RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
  - Prevent RV GE due to virus types heterologous to vaccine strain from two weeks after Dose 2 until the end of the first efficacy follow-up period.
  - Prevent any and severe pure RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
  - Prevent mixed RV GE (GE associated with RV and at least one other pathogen) during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
  - Prevent any hospitalization for RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.

For the subset of subjects who received three doses of HRV or placebo:

- To explore the rates of any and severe RV GE during the period starting from 2 weeks after Dose 3 until the end of the first efficacy follow-up period.

Second efficacy follow-up period (for a subset of approximately 1000 subjects)

- To evaluate the efficacy of the HRV vaccine during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period, and during the period starting from 2 weeks after the last HRV/placebo dose until the end of the second efficacy follow-up period.

Safety/Reactogenicity

- To assess the safety and reactogenicity of two doses of GSK Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo.
- To assess the safety and reactogenicity of the third dose of GSK Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations compared with placebo in a subset of subjects.

Immunogenicity

For the subset of subjects planned to receive two doses of HRV or placebo:

- To assess vaccine take, in subjects previously uninfected with RV before vaccination, two months after each study vaccine dose in the stool analysis subset.
- To assess persistence of serum IgA to RV at the end of the first efficacy follow-up period.
- To explore in a subset of subjects the effect of GSK Biologicals' HRV vaccine on the immune response to concurrently administered routine vaccinations.
- To explore the effect of unrestricted feeding on the immunogenicity of the vaccine.
- To assess viral shedding in the vaccine groups in the stool analysis subset.

For the subset of subjects who received three doses of HRV or placebo:

- To assess serum IgA to RV, two months after Dose 2 and Dose 3 of study vaccine or placebo.
- To assess viral shedding in the vaccine groups after the third HRV vaccine dose.
- To explore the effect of GSK Biologicals' HRV vaccine on the immune response to concurrently administered routine vaccinations two months after the third dose of routine vaccines.

See Section 3.15.2 for delineation of secondary endpoints.

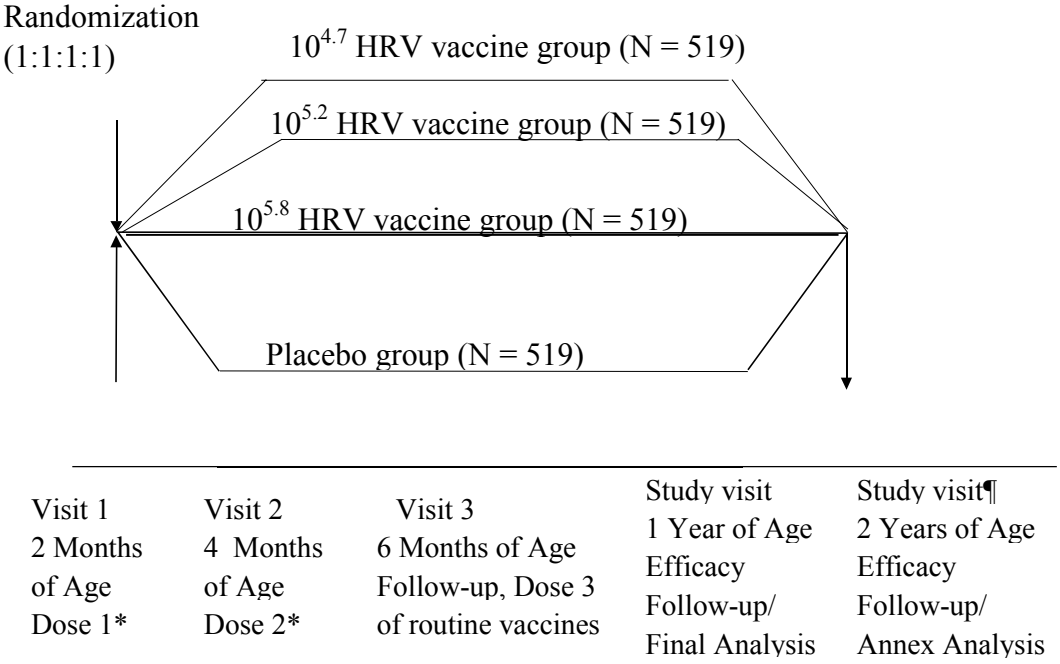
3 Methodology

Appendices: Study Information contains the study protocol, a representative subject information sheet and unique pages of the individual electronic Case Report Forms (eCRFs) utilized in the study.

3.1 Study design

Experimental design

For the subset of subjects planned to receive two doses of HRV vaccine or placebo:

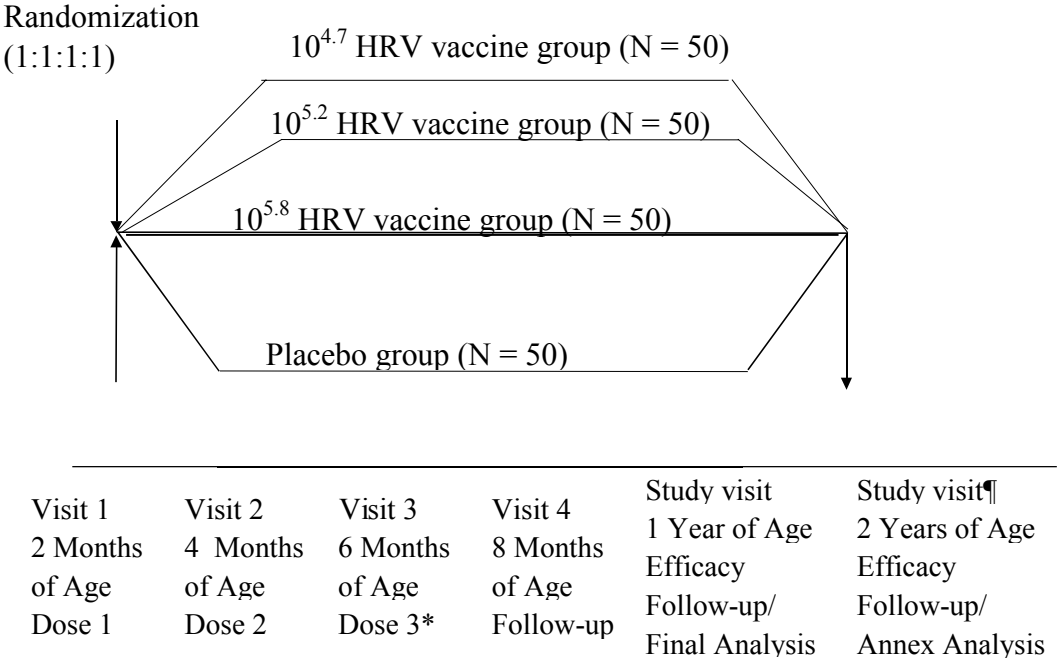


N = planned number of subjects

* HRV vaccine or placebo and concomitant routine vaccines

¶In a subset of subjects

For the subset of subjects who received three doses of HRV or placebo:



N = planned number of subjects

*HRV vaccine or placebo and concomitant routine vaccines

¶In a subset of subjects

This was a double-blind, randomized, placebo-controlled study consisting of four parallel groups with balanced allocation (1:1:1:1). The parents or guardians of the subjects and the study personnel (the investigator, study nurses and other personnel from the investigator's team who were involved in the study) were unaware of the administered treatment (HRV vaccine or placebo) during the entire study period until study end.

Data collection was performed using remote data entry (RDE).

Administration of Hepatitis B vaccine (HBV), Bacillus Calmette-Guerin (BCG) vaccine and OPV at birth was allowed according to local Expanded Program of Immunization (EPI) and was to be recorded in the eCRF.

There were no restrictions on feeding the infants before or after study vaccine or placebo administration.

Information on feeding on the day of each study vaccine administration was recorded for all subjects. The parents/guardians were questioned whether the child was fed with breast milk or infant formula and whether the child was fed within 60 minutes before study vaccination and/or within 30 minutes after study vaccination.

Subjects receiving two doses of HRV vaccine or placebo were to receive routine vaccinations (DTPw-HB+Hib vaccine) concomitantly with the study vaccines at 2 and 4 months of age; thereafter, DTPw-HB+Hib vaccine was to be given at 6 months of age.

Subjects receiving three doses of HRV vaccine or placebo were to receive routine vaccinations (DTPw-HB+Hib vaccine) concomitantly with each dose of HRV vaccine or placebo.

OPV was to be given at the discretion of the investigator, but was not to be administered during the period starting 2 weeks before each dose of HRV vaccine or placebo and ending 2 weeks thereafter.

Administration of all routine vaccinations, including OPV, was to be documented in the eCRF.

All subjects were followed for efficacy until approximately one year of age.

A subset of approximately 1000 subjects participated in the second efficacy follow-up period (until maximum age 24 months). The second efficacy follow-up period in Mexico ended in June 2003 (after the end of the 2003 RV season). The second efficacy follow-up period in Brazil and Venezuela ended in October 2003.

For the subjects who participated only in the first efficacy follow-up period (until approximately one year of age), the intended duration of the study, per subject, was approximately 10 months.

For the subset of subjects who participated in a second efficacy follow-up period, the intended duration of the study, per subject, was 22 months at most.

An Independent Data Monitoring Committee (IDMC) was monitoring the safety aspects of the HRV vaccine clinical development: i.e. each Serious Adverse Event (SAE) or Intussusception (IS) case was reviewed by this committee.

3.2 Investigators and trial centres

Appendices: Study Information contains the *curriculum vitae* of the principal investigators.

This multicentre study was conducted independently in Brazil, Mexico and Venezuela.

Table 1 provides the GSK assigned centre numbers, investigational sites and investigators in each country.

Table 1: The GSK assigned centre numbers, investigational sites and investigators

GSK assigned centre number	Investigational site	Principal Investigators	Co-investigators
[redacted]	[redacted] Brasil	Dr. [redacted] M.D., Ph.D.	Dr. [redacted] B.Sc, Ph.D. Dr. [redacted] M.D. Dr. [redacted] M.D. Dr. [redacted] M.D. Dr. [redacted] M.D.
[redacted]	[redacted] México,	Dr. [redacted] M.D.	Dra. [redacted] M.D., M.S.
[redacted]	[redacted] Venezuela	Dra. [redacted] M.D. Dra. [redacted] Ph.D as the Principal Study Co-ordinator	Dra. [redacted] M.D. Dra. [redacted] M.D.

3.3 Ethics

The study was conducted according to Good Clinical Practices (GCP) and in accordance with the Declaration of Helsinki as amended in Somerset West, Republic of South Africa in October 1996.

Written informed consent was obtained from each subject's parent or guardian prior to entry into the study.

Standardized eCRFs were provided for each subject's data to be recorded.

The study protocol dated October 20, 2000 and the statement of informed consent were approved by the Ethics Committees mentioned in Table 2 as well as the Ministry of Health (MOH) in each country prior to study initiation.

Table 2: Ethics Committees for each centre

Study centre	Ethics Committees
Brazil	[redacted] Brasil
Mexico	[redacted] México,
Venezuela	[redacted] Venezuela

All subsequent amendments were also submitted to the above-mentioned Ethics Committees and the changes to the protocol were implemented after approvals from the respective Ethics Committees' were obtained.

All submitted amendments were approved, except for Amendment 3 in Venezuela (see Section 3.3.1 for information on Amendment 3). The amendment was rejected since the Ethics Committee in Venezuela felt that administration of an additional dose (third dose of HRV vaccine or placebo) would affect the reputation of the principal investigator since over 90% of the subjects would be part of the two-dose subset and only a small number of subjects (approximately 45 subjects) would be part of the three-dose subset.

3.3.1 Protocol amendments/modifications

Amendment 1: The first amendment dated February 12, 2001 was done to correct the actual release titer of one of the clinical lots used in this study, to direct parents/guardians to contact study personnel for every case of GE, to define the subsets for serum and stool analyses, delete GE stool testing for cryptosporidia and to clarify the use of several commercial lots for the routine vaccines.

Modification 1: The first modification dated May 14, 2001 was done to implement changes in study personnel in Brazil and Venezuela.

Site-specific amendment for Venezuela: The site-specific amendment dated October 10, 2001 was done to evaluate fecal RV IgA immune response and the role of IgA antibodies as marker of protection against RV disease in a subset of 200 infants from Venezuela. Analysis and reporting of the data from tests performed on the additional stool samples from the subset of 200 subjects in Venezuela is the responsibility of Dra. [redacted] the principal investigator in Venezuela. A separate report will present data obtained during the site-specific evaluation.

Amendment 2: The second amendment dated December 11, 2001 was done to allow termination of enrolment in Mexico by end December 2001 to avoid vaccinating subjects during the RV season and to change the addresses of the GSK offices in Brazil and Mexico.

Amendment 3: The third amendment dated May 3, 2002 was done to allow administration of a third dose of the HRV vaccine or placebo to a subset of 200 infants in order to explore a three-dose schedule and to decrease the sample size from 2640 subjects to 2276 subjects because of difficulty in enrolling eligible subjects for participation in the study.

Amendment 4: The fourth amendment dated July 11, 2002 was done to allow an interim analysis in order to provide early information on the efficacy of the HRV vaccine against any and severe RV GE in Latin America.

Amendment 5: The fifth amendment dated September 20, 2002 was done to add a second efficacy follow-up period (until maximum age 24 months) for the subjects who had not completed the study as of October 31, 2002.

Amendment 6: The sixth amendment dated March 26, 2003 was done to implement the use of a ‘Standard Verbal Autopsy Questionnaire’ as per the IDMC's recommendation, to remove co-pathogen testing for all subjects during the second efficacy follow-up period, to allow termination of follow-up of Mexican subjects after the end of the 2003 RV season in Mexico and to allow an interim efficacy analysis at the end of the second efficacy follow-up period in Mexico.

Amendment 7: The seventh amendment dated August 21, 2003 was done to allow study end in October 2003 by terminating the second efficacy follow-up of subjects in Brazil and Venezuela.

Annex Study 444563(rota)008 in Mexico: Additionally, an annex protocol dated November 29, 2000 was implemented in Mexico (study rota-008) to characterize the immune response of the HRV vaccine in subjects participating in study rota-006 in Mexico. The aim of the study was to assess the impact of breast-milk lactadherin, breast-milk anti-rotavirus IgA antibodies and maternal IgG antibodies on immunogenicity of the HRV vaccine. Mothers of approximately 200 subjects, who were enrolled in study rota-006 and were part of the subset providing blood samples at post-vaccination timepoints, participated in study rota-008. The analyses for transplacental anti-rotavirus IgG antibodies and transplacental anti-rotavirus neutralizing antibodies in study rota-008 are available and are presented in the report "The Interference of Transplacental Antibodies on Response to GSK Biologicals' Human Rotavirus Vaccine: Rota-004, Rota-008 and Rota-014". A separate report will present all data on characterization of the immune response of the HRV vaccine.

3.4 Selection of study population

The study population consisted of healthy male and female infants enrolled after checking the eligibility criteria at study entry.

3.4.1 Inclusion criteria

The following criteria were checked at the time of study entry.

- A male or female between, and including, 6 and 12 weeks (42–90 days) of age at the time of the first vaccination.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Written informed consent obtained from the parents or guardians of the subject.
- Born after a normal gestation period (between 36 and 42 weeks) or with a birth weight > 2000 g.

3.4.2 Exclusion criteria

The following criteria were checked at the time of study entry. If any applied at the time of study entry, the infant was not included in the study:

- Use of any investigational or non-registered drug or vaccine other than the study vaccine within 30 days preceding the study vaccine or placebo or planned use during the study period.

- Planned administration of a vaccine (including routine paediatric vaccines) not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine and ending 14 days after.
- Planned administration of OPV during the period starting from 2 weeks before each dose of study vaccine and ending 2 weeks after.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth. (Topical steroids were allowed.)
- History of previous diphtheria, tetanus, pertussis, Hib disease and/or hepatitis B.
- Previous vaccination against diphtheria, tetanus, pertussis and/or Hib.
- Use of antibiotics within 7 days preceding Dose 1 of study vaccine (warranted deferral of vaccination pending recovery of the subject).
- Any clinically significant history of chronic gastrointestinal disease including any uncorrected congenital malfunction of the gastrointestinal tract or other serious medical condition as determined by the investigator.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
- History of allergic disease or reaction likely to be exacerbated by any component of the vaccine.
- Acute disease at time of enrolment. (Acute disease was defined as the presence of moderate or severe illness with fever i.e. temperature ≥ 37.5°C as measured by an axillary thermometer or ≥ 38.0°C as measured by a rectal thermometer). A temperature greater than or equal to these cut-offs warranted deferral of vaccination pending recovery of the subject.
- GE within 7 days preceding the study vaccine administration (warranted deferral of the vaccination).
- Household contact with an immunosuppressed individual or pregnant woman.
- Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
- Previous confirmed occurrence of RV GE.

3.4.3 Elimination criteria during the study up to Visit 3 (up to Visit 4 for the subset of subjects receiving three doses of study vaccine or placebo)

The following criteria were checked at Visits 2 and 3. These elimination criteria were also checked on the day of Dose 3 of the study vaccine or placebo in a subset of subjects (at Visit 4). If any became applicable during the study, the subject was not required to discontinue the study but could be eliminated from the according-to-protocol (ATP) cohort analyses.

- Use of any investigational or non-registered drug or vaccine other than the study vaccine during the study period.

- Use of antibiotics during the period starting from 7 days before Dose 1 and 2 of study vaccine and ending 7 days after.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids are allowed.)
- Administration of a vaccine (including routine paediatric vaccines) not foreseen by the study protocol during the period starting from 14 days before each dose of study vaccine(s) and ending 14 days after.
- Administration of OPV during the period starting from 2 weeks before each dose of study vaccine and ending 2 weeks after.
- Administration of immunoglobulins and/or any blood products during the study period.
- Confirmed immunosuppressive or immunodeficient condition, including HIV.

3.4.4 Elimination criteria during the study from Visit 3 (from Visit 4 for the subset of subjects receiving three doses of study vaccine or placebo) until study end

If any became applicable during the study, the subject was not required to discontinue the study but could be eliminated from the ATP cohort analyses.

- Use of any investigational or non-registered drug or vaccine other than the study vaccine during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs during the study period. (Topical steroids were allowed.)
- Administration of immunoglobulins and/or any blood products during the study period.
- Confirmed immunosuppressive or immunodeficient condition, including HIV.

3.4.5 Contraindications to vaccination

GSK Biologicals' HRV vaccine or placebo

The following adverse events (AEs) constituted absolute contraindications to further administration of GSK Biologicals' HRV vaccine or placebo; if any of these AEs occurred during the study, the subject did not receive additional doses of HRV vaccine or placebo but could continue other study procedures at the discretion of the investigator. The subject was followed until resolution of the event, as with any AE:

- Hypersensitivity reaction due to the vaccine.
- Intussusception (IS).

The following AEs constituted contraindications to administration of HRV vaccine or placebo at that point in time; if any one of these AEs occurred at the time scheduled for vaccination, the subject could be vaccinated at a later date, within the time window specified in the protocol, or withdrawn at the discretion of the investigator. The subject was followed until resolution of the event, as with any AE:

- Axillary/rectal temperature ≥ 37.5/38.0°C.
- GE within 7 days preceding the study vaccine administration.

Routine DTPw-HB+Hib vaccine

The following AEs constituted absolute contraindications or precautions to further administration of routine DTPw-HB+Hib vaccine; if any of these AEs occurred during the study, the subject was withdrawn and followed until resolution of the event, as with any AE:

- Known hypersensitivity to any component of the vaccine or subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B or Hib vaccines.
- Encephalopathy (not due to another identifiable cause). This was defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination and generally consisting of major alterations in consciousness, unresponsiveness, and/or generalized or focal seizures that persisted more than a few hours, with failure to recover within 24 hours. Even though causation by DTP-containing vaccine has not been established, no subsequent doses of pertussis vaccine were to be given.

If the following AEs occurred in temporal relation to DTPw-HB+Hib vaccine administration, the decision to administer additional doses of DTPw-HB+Hib vaccine was to be carefully considered:

- Fever ≥ 40.5°C/≥ 40.0°C (rectal/axillary temperature) within 48 hours of vaccination not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting >3 hours, occurring within 48 hours of vaccination.
- Seizures with or without fever occurring within 3 days of vaccination.

3.5 Study vaccines and administration

The study vaccines used were developed and manufactured by GSK Biologicals, Belgium.

The Quality Control Standards and Requirements for each vaccine are described in separate release protocols and the required approvals were obtained. The vaccine release protocols are archived in the study file and are available upon request.

3.5.1 GSK Biologicals' HRV vaccine

One dose of lyophilized HRV vaccine contained the following components:

RIX4414 (derived from the 89-12 HRV strain)	$10^{4.7}$ ffu, $10^{5.2}$ ffu or $10^{5.8}$ ffu
Sucrose	9 milligram (mg)
Dextran	18 mg
Sorbitol	13.5 mg
Amino acids	9 mg

Lot number DRVC005A46 was used for HRV vaccine $10^{4.7}$ ffu.
Lot number DRVC010A48 was used for HRV vaccine $10^{5.2}$ ffu.
Lot number DRVC004A46 was used for HRV vaccine $10^{5.8}$ ffu.

3.5.2 GSK Biologicals' placebo for HRV vaccine

One dose of lyophilized placebo contained the following components:

Sucrose	9 mg
Dextran	18 mg
Sorbitol	13.5 mg
Amino acids	9 mg

Lot numbers DRVC014A48PL and DRVC006A46PL were used.

3.5.3 GSK Biologicals' calcium carbonate buffer used as diluent

Each pre-filled syringe of 1.3 ml in volume contained the following components per 1.0 ml:

Calcium carbonate	60 mg
Xanthane 0.25 % in water for injection	1.0 ml

Lot numbers 00J03/1010, 00I19/1006, 00J03/1010, 00J04/1011 and 01C09/1013 were used for the diluent.

3.5.4 Dosage and administration

The HRV vaccine or placebo was prepared for administration by injecting the entire content of one pre-filled syringe containing the calcium carbonate buffer into the vial of the lyophilized product (vaccine or placebo). The vial was shaken well to

resuspend the vaccine/placebo. The entire volume of the resuspended product was withdrawn into the same syringe, the needle discarded and the resuspended product administered promptly as a single oral dose (approximately 1.0 ml).

Subjects received two doses of the reconstituted HRV vaccine or its placebo orally at Visits 1 and 2. A subset of subjects received a third dose of the reconstituted HRV vaccine or its placebo orally at Visit 3.

The subjects were observed closely for at least 30 minutes, with appropriate medical treatment readily available, in case of a rare anaphylactic reaction following the administration of vaccine.

3.6 Routine vaccines and administration

Commercially available routine vaccines were assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics.

3.6.1 GSK Biologicals' DTPw-HB+Hib vaccine

The DTPw-HB+Hib vaccine was supplied as two individual components, liquid DTPw-HB vaccine and lyophilized Hib vaccine, in monodose vials.

One dose (0.5ml) of DTPw-HB vaccine contained the following components:

Active ingredients	
Bordetella pertussis, killed	not less than 4 International Units (IU) (Lower Confidence Limit (LCL): not less than 2 IU) [15 Opacity Units (OU)]
Diphtheria toxoid	LCL not less than 30 IU (7.5 Limit Floculation (Lf))
Tetanus toxoid	LCL not less than 60 IU (3.25 Lf)
Recombinant DNA Hepatitis B virus surface antigen	10 microgram (mcg)
Other ingredients	
2-phenoxyethanol	0.5 mg
Aluminium as aluminium phosphate and aluminium hydroxide	0.63 mg
Sodium chloride	4.5 mg
Thiomersal	25 mcg
Water for injection	ad 0.5 ml

One dose (0.5ml) of Hib vaccine contained the following components:

Active ingredients

Conjugate of 10 mcg *Haemophilus influenzae* type b capsular polysaccharide, polyribosyl ribitol phosphate (PRP), and tetanus toxoid

Excipient

Lactose	12.6 mg

Commercial lots of DTPw-HB and Hib vaccines were used.

3.6.2 GSK Biologicals' OPV (Polio Sabin) vaccine

OPV vaccine was supplied as a liquid preparation. One dose (0.5ml) of OPV vaccine contained the following components:

Poliovirus type 1 (LS-c, 2ab)	not less than 10^6 to $10^{6.5}$ $CCID_{50}$
Poliovirus type 2 (P712, Ch, 2ab)	not less than 10^5 to $10^{5.5}$ $CCID_{50}$
Poliovirus type 3 (Leon $12a_1b$)	not less than $10^{5.8}$ to 10^6 $CCID_{50}$
Magnesium chloride	20.33 mg
Neomycin	≤ 5 µg

$CCID_{50}$ = median Cell Culture Infective Dose (quantity of virus causing infection in 50% of exposed cells)

Commercial lots of OPV vaccine were used.

3.6.3 Dosage and administration

The DTPw-HB+Hib vaccine was to be prepared according to the manufacturer's recommendations and administered intramuscularly into the anterolateral thigh using a 23- or 25- gauge needle. Subjects were to receive one dose (0.5 ml) of DTPw-HB+Hib vaccine at Visits 1, 2 and 3.

The OPV vaccine was prepared according to the manufacturer's recommendations. Three doses of OPV were to be given at the discretion of the investigator, but were not to be administered during the period starting 2 weeks before each dose of study vaccine or placebo and ending 2 weeks after.

3.7 Treatment allocation and randomization

3.7.1 Randomization of supplies

A randomization list was generated at GSK Biologicals, Rixensart, Belgium using a standard SAS® (Statistical Analysis System) program to number vaccine doses.

A randomization blocking scheme (1:1:1:1 ratio) was used to ensure that balance between treatments was maintained: a unique randomization number identified the vials to be administered to the same subject. The vaccine doses were distributed to the study sites while respecting the randomization block size.

To allow GSK Biologicals' to take advantage of greater than anticipated rates of recruitment at individual centres in this multicentre study, and to reduce the overall study recruitment period, a 10% over-randomization of supplies was prepared. However, enrolment was terminated when the target sample size was reached.

3.7.2 Randomization of subjects

All study centres used a central randomization system using the Internet, except in case of unexpected technical problems, to randomly allocate eligible subjects to a study group. The randomization algorithm used a minimisation procedure stratified by centre ([3]). When central randomization was not possible due to unexpected technical problems, manual randomization took place (selecting the higher patient identification numbers (PIDs) available).

Each subject was given vaccine doses identified with the unique randomization (or vaccine) number assigned to him/her. The vaccine number was also used as PID for all data collected for the subject during the study.

3.7.3 Subset definition

Subsets to evaluate immunogenicity of two doses of HRV vaccine or placebo
A subset of approximately 800 subjects were planned to provide blood samples at Visits 2 and 3 and an additional amount of blood at study visit at the end of the first efficacy follow-up period. The first 200 enrolled subjects in each participating country constituted this subset. The remaining 200 subjects in this subset were included according to the order of enrolment irrespective of their country.

Stool analysis subset
A subset of approximately 400 subjects were planned to provide stool samples on the day of Dose 1 and Dose 2, and on Day 7±1 following each dose of HRV vaccine or placebo. The first 100 enrolled subjects in each participating country constituted this subset. The remaining 100 subjects in this subset were included according to the order of enrolment irrespective of their country. The approximately 400 subjects constituting the stool analysis subset were part of the subset providing blood samples at Visits 2 and 3. This subset was used to calculate vaccine take since serology and shedding data were both available only for this subset.

Subset receiving three doses of HRV vaccine or placebo
A subset of 200 subjects from Brazil and Venezuela was planned to receive a third dose of HRV vaccine or placebo at 6 months of age (at Visit 3). As the protocol was not approved in Venezuela, this subset only constituted the last 121 subjects enrolled in Brazil. This subset provided blood samples at Visit 3 (day of Dose 3 of HRV vaccine or placebo) and at Visit 4 (two months after Dose 3 of HRV vaccine or placebo). This subset also provided stool samples on the day of and on Day 7±1 after Dose 3 of HRV vaccine or placebo.

Subset followed for efficacy until maximum 24 months of age
All subjects who had not completed the follow-up visit at one year of age as of October 31, 2002 were part of the subset (N = approximately 1000) to be followed for efficacy during the second efficacy follow-up period (until maximum age 24 months). This subset had an additional study visit at the end of the second efficacy follow-up period for GE follow-up. The second efficacy follow-up period in Mexico ended in June 2003 (after the end of the 2003 RV season). In Brazil and Venezuela, the second efficacy follow-up period ended in October 2003.

3.8 Blinding

This study was conducted in a double-blind manner. The parents or guardians of the subjects and the study personnel were unaware of the administered treatment (HRV vaccine or placebo) during the entire study period until study end.

Selected persons (not part of the investigative or sponsor clinical teams) using the central randomization system could perform unblinding. The code could be broken by the Clinical Safety Physician only in the case of medical events, which the investigator or physician in charge of the subject felt could not be treated without knowing the identity of the study vaccine.

The IDMC had access to the individual treatment codes and could at its discretion identify the product administered to any subject to evaluate whether enrolment in the study had to be halted.

In the event that the code was broken, the reason was recorded in the eCRF and in the subject's medical record.

During analysis at the end of the first efficacy follow-up period, only the statistician and database administrator had access to the individual treatment code for all subjects. In addition, access to the individual treatment code for some subjects was made available within GSK personnel, after the database was frozen for the analysis at the end of the first efficacy follow-up period, for the purpose of interim analyses of the research protocols related to study rota-006.

Moreover, access to the individual treatment code was made available for all SAEs after the database was frozen for the analysis at the end of the first efficacy follow-up period.

In this study report, only summary results without the individual subjects' treatment code (except for SAEs) are provided and individual subjects' numbers are not specified.

3.9 Study procedures

The study procedures carried out at each visit are given in Table 3.

Table 3: Outline of study procedures

Age	**2 months**	**4 months**	**6 months**	**8 months**	**1 year**	**18-24 Mo**
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4 Dose 3 subset only***	**End of 1st Efficacy Period**	**End of 2nd Efficacy Period**
Sampling timepoint	Pre	Post vacc 1	Post vacc 2 M4	Post vacc 3 M6	Post vacc 2 M10	
Informed consent	•					
Medical history	•					
Check of inclusion criteria	•					
Check of exclusion criteria	•					
Check of elimination criteria		•	•	•	•	•
Check of contraindications	•	•	•			
Physical examination	•	•	•	•	•	•
Pre-vaccination body temperature	•	•	•			
Measure/record height and weight	•	•	•	•	•	•
Blood sampling	• (1 ml)	• (1 ml#)	• (3 ml#) • (1 ml*)	• (3 ml*)	• (3 ml#, 1 ml)	
Randomization	•					

Source: Protocol and sample eCRF in *Appendices: Study Information*
Notes: #Subset *Subset receiving three doses of HRV vaccine/placebo
¶For subjects who participated only in the first efficacy follow-up period
§For subjects who participated in a second efficacy follow-up period

Table 3 (continued): Outline of study procedures

Age	2 months	4 months	6 months	8 months	1 year	18-24 Mo
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4***	**End of 1st Efficacy Period**	**End of 2nd Efficacy Period**
Sampling timepoint	Pre	Post vacc 1	Post vacc 2 M4	Post vacc 3 M6	Post vacc 2 M10	
Stool samples will be collected from a subset (N = 400) on the day of administration of Dose 1 and Dose 2 and on Day 7±1 following each study vaccine dose. Stool samples will be collected from a subset (N ~ 200) on the day of administration of Dose 3 and on Day 7±1 following Dose 3 of study vaccine	•	•	•*			
Study Vaccine	•	•	•*			
Routine Vaccination	•	•	•			
Daily post-vaccination recording of solicited symptoms (Days 0–14) by parents/guardians	•	•	•*			
Collection of stool samples if the child is suspected to have GE	•	•	•	•	•	•
Recording of solicited symptoms, non serious AEs within 43 days after Dose 1, Dose 2 and Dose 3 (in a subset) of study vaccine, by the investigator		•	•	•*		
Contact (field visit) every week	◊	◊	◊	◊	◊	◊
Return of GE diary	•	•	•	•*	•	•
GE diary transcription		•	•	•*	•	•
Documentation of routine EPI vaccines	•	•	•	•*	•	•
Recording medication	•	•	•	•*		
Reporting of SAEs occurring throughout the study period	•	•	•	•*	•	•
Study Conclusion					•¶	•§

Source: Protocol and sample eCRF in *Appendices: Study Information*
Notes: *Subset receiving three doses of HRV vaccine/placebo
◊ is used to indicate a study procedure which does not require documentation in the individual eCRFs
¶For subjects who participated only in the first efficacy follow-up period
§For subjects who participated in a second efficacy follow-up period

3.10 Subject completion and drop out

From an analysis perspective, a 'drop out' was any subject who did not come back for the concluding visit foreseen in the protocol. A subject who returned for the concluding visit foreseen in the protocol was considered to have completed the study.

Investigators attempted to contact those subjects who did not return for scheduled visits or follow-up. Information gathered was described on the Study Conclusion page of the eCRF and on Medication/AE forms. The possible reasons responsible for drop out of the subject from the study were specified on the Study Conclusion page of the eCRF and were as follows:

- SAE
- Non-serious AE
- Protocol violation (specify)
- Consent withdrawal, not due to an AE
- Migration from the study area
- Lost to follow-up
- Other (specify)

Study drop outs were not replaced.

3.11 Assessment of efficacy variables

An active surveillance for GE (defined as diarrhea) was conducted *via* weekly visit to each subject by study personnel (Health Workers) starting 1 week after Dose 1 of HRV vaccine or placebo and ending at the final study visit foreseen for that subject. All subjects were followed for efficacy until approximately one year of age. A subset of approximately 1000 subjects participated in the second efficacy follow-up period (until maximum age 24 months).

The weekly follow-up by the Health Worker took place at the subject's home, at a health clinic or other mutually convenient place. Health Workers inquired about occurrence of diarrhea at the weekly visits. Weekly visit by the Health Worker did not take place in weeks when a study clinic visit was scheduled.

The parents or guardians were instructed to contact study personnel whenever they suspected that the subject had diarrhea during the study. If diarrhea occurred during the solicited follow-up period (Day 0–Day 14 of each study vaccination), the information regarding the diarrhea episode was to be recorded on the reactogenicity diary card by the parents/guardians. If the diarrhea started during the solicited follow-up period and ended after the solicited follow-up period, the GE diary card was to be completed by the parents/guardians in addition to the reactogenicity diary card. The GE diary card was to be completed by the parents/guardians during each suspected episode of diarrhea that started outside the solicited follow-up period. On each day during a suspected episode of diarrhea, number of looser than normal stools, axillary/rectal temperature and number of vomiting episodes were recorded by the parents/guardians on the GE diary card until the end of the GE episode. Rehydration or other medications were also recorded. During weekly visits, the Health Worker ensured that the diary card was being properly completed and collected the completed diary cards. The investigator checked the completed diary cards and transcribed data into the appropriate sections of the eCRFs.

Parents/guardians of all subjects were instructed to collect one stool sample within 7 days of onset of each suspected diarrhea episode. A second stool sample was to be collected on a different day if the first stool sample was not sufficient. The time interval for stool sampling was adapted prior to analysis. Stool samples collected from the start of the GE episode to the minimum of the following 2 timepoints either 7 days after the end of the GE episode or the day before the next GE episode if subject had several episodes of GE were used to identify an episode of RV GE. Parents/guardians were given instructions to be followed for appropriate collection, storage and transportation of the stool samples. If required, Health Workers collected a stool sample during weekly visits. The Health Workers organized transportation of the stool samples.

Two occurrences of diarrhea were classified as separate episodes if there were 5 or more symptom-free days between the episodes.

A 20-point scoring system was used to assess the severity of each diarrheal episode ([4]). Refer to Table 4 for the scoring system used to assess the severity of each diarrhea episode using data collected *via* eCRFs.

Table 4: The 20-point scoring system used to assess the severity of each diarrhea episode

Adverse Experience	Points
Duration of looser than normal stools (days)	
1–4	1
5	2
≥ 6	3
Maximum number of looser than normal stools/24 hours	
1–3	1
4–5	2
≥ 6	3
Duration of vomiting (days)	
1	1
2	2
≥ 3	3
Maximum number of episodes of vomiting/24 hours	
1	1
2–4	2
≥ 5	3
Fever (measured rectally/axillary)*	
37.1–38.4°C/36.6-37.9°C	1
38.5–38.9°C/38.0-38.4°C	2
≥ 39°C/≥ 38.5°C	3
Treatment	
Rehydration	1
Hospitalization	2
Dehydration	
1–5 %	2
≥ 6%	3

Comments: * The highest temperature recorded during the episode was scored.

Points were assigned at GSK Biologicals according to duration and intensity of diarrhea and vomiting, the intensity of fever, presence of dehydration or hospitalization for each episode. Subjects with only fever or only vomiting did not receive a score.

A score of < 7 was prospectively defined as mild, a score of 7–10 was prospectively defined as moderate and a score ≥ 11 was prospectively defined as severe ([5]).

3.11.1 Diarrheal stool analysis

All stool samples collected during any episodes of diarrhea were analyzed locally using a commercially available rapid RV detection kit, RotaClone™ (Meridian Diagnostics Inc.). If RV was detected locally using RotaClone™ in a stool sample collected during the first efficacy follow-up period, an aliquot of the stool sample was analyzed locally for culture of enteric pathogens such as Salmonella, Shigella, and Campylobacter. Presence of Enteroaggregative *Escherichia coli* and Enteroinvasive *Escherichia coli* was tested at the laboratory of Dr. [redacted] Mexico.

All stool samples collected during any episodes of diarrhea, irrespective of results of the local RV (RotaClone™) tests, were tested centrally by Enzyme Linked Immunosorbent Assay (ELISA) ([1], [2]) at the Laboratory of Dr. [redacted] Children's Hospital Medical Centre, Cincinnati, USA to detect the presence of RV (refer to *Appendix C: Laboratory assays*). Only diarrheal stool analysis performed at the Laboratory of Dr. [redacted] Children's Hospital Medical Centre, Cincinnati, USA was considered for the efficacy analyses.

Efficacy estimates against severe RV GE were similar using locally-performed RotaClone™ test and centrally-performed ELISA test for detection of RV in stool samples. An overall agreement of 97% was also observed between the two RV detection methods.

All stool samples that were RV positive by centrally-performed ELISA were tested by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) at GSK Biologicals, Rixensart, Belgium to determine the G type (refer to *Appendix C: Laboratory assays*). If any G1 RV was detected in the stool samples collected between Visit 1 to Visit 3 (Visit 4 for subjects receiving three doses of HRV vaccine or placebo), vaccine virus was differentiated from wild-type RV by sequence analysis.

3.12 Assessment of safety variables

Pre-existing conditions, signs and/or symptoms (including any which were not recognized at study entry but were recognized during the study period) present in a subject prior to the start of the study were recorded on the Medical History Form within the subject's eCRF. AEs which occurred after informed consent was obtained, but prior to vaccination, were also documented in the Medical History Form within the subject's eCRF.

At each visit/assessment, all AEs either observed by the investigator or one of his clinical collaborators or reported by the subject spontaneously or in response to a direct question were evaluated by the investigator. AEs not previously documented in the study were recorded in the AE Form within the subject's eCRF. Details of any corrective treatment were recorded on the appropriate page of the eCRF. AEs already documented in the eCRF, i.e. at a previous assessment, and designated as 'ongoing' were reviewed at subsequent visits, as necessary. If these had resolved, the documentation in the eCRF was completed.

The parents/guardians were instructed to contact the investigator immediately if the subject manifested any signs or symptoms during the study that they perceived as serious.

Reactogenicity diary cards were distributed to the parents/guardians on the day of each study vaccination to record solicited AEs occurring during the 15-day (Day 0 to Day 14) solicited follow-up period. Intensity of the solicited AEs was assessed as described in Table 5.

Table 5: Intensity scales for solicited symptoms

Adverse Event	**Intensity grade**	**Parameter**
Diarrhea		Number of looser than normal stools/day recorded
Fever*		Temperature recorded rectally or axillary in °C
Irritability/fussiness	0	Behaviour as usual
	1	Crying more than usual/ no effect on normal activity
	2	Crying more than usual/ interferes with normal activity
	3	Crying that cannot be comforted/ prevents normal activity
Loss of appetite	0	Normal
	1	Eating less than usual/ no effect on normal activity
	2	Eating less than usual/ interferes with normal activity
	3	Not eating at all
Vomiting		Number of vomiting episodes/day recorded.
Cough/runny nose	0	Normal
	1	Cough/runny nose which is easily tolerated
	2	Cough/runny nose which interferes with daily activity
	3	Cough/runny nose which prevents daily activity

Comments: *Rectal /axillary temperature was recorded in the evening. If temperature measurement was performed additionally at another time of day, the highest temperature was recorded.

Health Workers ensured that the reactogenicity diary card was being properly completed by the parents/guardians, and collected the completed diary card. The investigator checked the completed diary cards and transcribed data into the appropriate sections of the eCRFs.

The maximum intensity of fever, diarrhea and vomiting were scored at GSK Biologicals as follows:

Diarrhea	0	:	0–2 looser than normal stools/day
	1	:	3 looser than normal stools/day
	2	:	4–5 looser than normal stools/day
	3	:	≥ 6 looser than normal stools/day

Fever			Measured rectally	Measured axillary
	0	:	< 38.0°C	< 37.5°C
	1	:	≥ 38.0 – ≤ 38.5°C	≥ 37.5 – ≤ 38.0°C
	2	:	> 38.5 – ≤ 39.5°C	> 38.0 – ≤ 39.0°C
	3	:	> 39.5°C	> 39.0°C

Vomiting	0	:	No emesis
	1	:	1 episode of vomiting/day
	2	:	2 episodes of vomiting/day
	3	:	≥ 3 episodes of vomiting/day

All other AEs occurring during the 43-day (Day 0 to Day 42) follow-up period after each vaccination were noted as unsolicited symptoms. Maximum intensity was assigned to one of the following categories:

1 : An AE which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2 : An AE which was sufficiently discomforting to interfere with normal everyday activities.

3 : An AE which prevented normal, everyday activities.
(Such an AE, for example, prevented attendance at school/kindergarten/day-care centre and caused the parents/guardians to seek medical advice.)

Every effort was made by the investigator to explain each AE and assess its causal relationship, if any, to administration of the study vaccine. The degree of certainty with which an AE could be attributed to administration of the study vaccines (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) was determined by how well the event could be understood in terms of one or more of the following:

- Reaction of similar nature having previously been observed with this type of vaccine and/or formulation.
- The event having often been reported in literature for similar types of vaccines.
- The event being temporally associated with vaccination or reproduced on re-vaccination.

Causality of all AEs was assessed by the investigator using the following question: In your opinion, did the vaccines possibly contribute to the AE?

NO : The AE was not causally related to administration of the study vaccine. There were other, more likely causes and administration of the study vaccine was not suspected to have contributed to the AE.

YES : There was a reasonable possibility that the vaccine contributed to the AE.

If an event met the criteria to be determined "serious" (see below for definition of serious adverse events (SAEs)), it was examined by the investigator to the extent to be able to determine ALL contributing factors applicable to each SAE. Other possible contributors included:

- Medical history
- Other medication
- Protocol required procedure
- Lack of efficacy of the vaccine
- Erroneous administration
- Other cause (to be specified)

A SAE was defined as any untoward medical occurrence that:

- resulted in death
- was life threatening
- resulted in persistent or significant disability/incapacity
- required in-patient hospitalization or prolongation of hospitalization
- was a congenital anomaly/birth defect in the offspring of a subject

In addition, any important medical event that might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above was also considered as serious.

The investigator was required to notify GSK Biologicals of any SAE starting from the day of administration of the first dose of HRV vaccine or placebo to each subject and ending at study end, within 24 hours of his/her becoming aware of the event. Following the telephone report, a full written report was to be provided which included all relevant supporting documentation such as hospital records, eventual post-mortem reports and/or other documents where applicable. The standard verbal autopsy questionnaire was to be completed and transmitted by the investigator or his designee, in addition to the SAE report, for all deaths during the study period irrespective of relationship to vaccination and whether a written autopsy report was available or not.

Parents/guardians were informed about symptoms consistent with IS namely severe colicky abdominal pain, persistent vomiting, bloody stools, abdominal bloating and fever up to 41° C and made aware that there could be possible increased risk of IS after vaccination. Parents/guardians were asked to contact the investigator if they noticed any symptoms indicative of IS. The investigator and his staff were also aware of the possible increased risk of IS and considered this diagnosis in children presenting symptoms indicative of IS. In case a subject was diagnosed with IS, immediate reporting to the sponsor was mandatory as for any SAE. The diagnosis of IS was to be documented by radiography. Detailed instructions on the evaluation of IS were provided to the investigator and his staff. The investigator was to take appropriate actions to evaluate and treat the condition. The investigator was required to document all available information for each IS case on the SAE pages in the eCRF. In addition, the investigator was required to complete the IS Form when all data became available and fax it to the GSK contact for SAE reporting. Each case of suspected or confirmed IS was reviewed by the IDMC.

Treatment of any AE was at the discretion of the investigator and according to current GCP. Treatment measures were reported in the appropriate pages of the eCRF. The investigator was to follow subjects with SAEs until the event subsided or until the condition stabilized. The investigator was to follow subjects with non-serious AEs until study conclusion for that subject.

The outcome of all AEs, non-serious and serious, was indicated as follows:
1: Recovered
2: Recovered with sequelae
3: Ongoing at subject study conclusion
4: Died
5: Unknown

3.12.1 Pregnancy

Not applicable.

3.12.2 Prior and concomitant medication

The investigator questioned the parents/guardians about any medication given to the subject at Visits 1, 2 and 3 (for all subjects) and at Visit 4 (for the subset receiving three doses of HRV vaccine or placebo).

Administration of the following treatments was recorded in the eCRF by the investigator if the medication was given within the specified time frames:

- Any immunosuppressants or other immune-modifying drugs or treatments administered at any time during the period starting 30 days prior to the first dose of HRV vaccine or placebo and ending at Visit 3 (Visit 4 for the subset receiving three doses of HRV vaccine or placebo).
- Any vaccine other than the study vaccine(s) administered at any time during the period starting at birth and ending at the last study visit.
- Any antibiotics administered within 7 days preceding each study vaccine/placebo administration and during the first 7 days after each study vaccine/placebo administration.
- Any antipyretics administered at any time during the period starting 30 days prior to the first dose of HRV vaccine or placebo and ending one month (minimum 30 days) after the last dose of HRV vaccine or placebo.

Any other concomitant medication administered prophylactically in anticipation of reaction to the vaccination were also recorded in the eCRF with trade name and/or generic name of the medication, total daily dose, route of administration, start and end dates of treatment and coded as 'Prophylactic'.

3.13 Assessment of immunogenicity variables

3.13.1 Intervals between study visits

To adequately assess the immune responses elicited by the vaccines, time intervals to be respected between visits for vaccination and blood sampling were detailed in the protocol (see Table 6 and Table 7).

Table 6: Intervals between study visits for subjects planned to receive two doses of HRV vaccine or placebo*

Interval	Size of interval
Visit 1→Visit 2	49– 83 days
Visit 2→Visit 3	49–83 days
Visit 3→Follow-up visit at the end of the first efficacy follow-up period	160–200 days

Comments: * = Date of the previous visit was the reference date.

Table 7: Intervals between study visits for subjects receiving three doses of HRV vaccine or placebo*

Interval	Size of interval
Visit 1→Visit 2	49–83 days
Visit 2→Visit 3	49–83 days
Visit 3→Visit 4	49–83 days
Visit 3→Follow-up visit at the end of the first efficacy follow-up period	160–200 days

Comments: * = Date of the previous visit was the reference date

Subjects outside the protocol-specified intervals between Visit 1–2 and Visit 2–3 were excluded from the ATP cohort for immunogenicity analysis for subjects planned to receive two doses of HRV vaccine or placebo (immunogenicity analysis performed only on the total vaccinated cohort for subjects receiving three doses of HRV vaccine or placebo).

3.13.2 Laboratory assays and timepoints

3.13.2.1 Stool analysis

For subjects planned to receive two doses of HRV vaccine or placebo: Stool samples were collected on the day of Dose 1 and Dose 2 and on Day 7±1 after Dose 1 and Dose 2 of HRV vaccine or placebo from stool analysis subset in subjects planned to receive two doses of HRV vaccine or placebo.

For subjects receiving three doses of HRV vaccine or placebo: Stool samples were collected on the day of Dose 3 and on Day 7±1 after Dose 3 of HRV vaccine or placebo from all subjects who received a third dose of HRV vaccine or placebo.

All stool samples collected at pre-determined timepoints were analyzed using ELISA to detect RV at the Laboratory of Dr. [redacted] Children's Hospital Medical Centre, Cincinnati, USA (refer to *Appendix C: Laboratory assays*).

If RV was detected in stool samples collected at pre-determined timepoints from subjects in the placebo group, G type was determined *post-priori* by RT-PCR at GSK Biologicals, Rixensart, Belgium.

Any detection of RV in stool collected after each vaccination at pre-determined time points was taken as evidence of a vaccine response (i.e. vaccine take), as long as the subject is negative for RV on the day of Dose 1 of HRV vaccine or placebo.

Stool samples were also collected from all subjects during each diarrheal episode occurring during the study period. Refer to Section 3.11.1 for analysis of diarrheal stool samples.

3.13.2.2 Serum analysis

For subjects planned to receive two doses of HRV vaccine or placebo:

A minimum of 1 ml of whole blood was collected from all subjects at Visit 1 (on the day of Dose 1 of HRV vaccine or placebo) to test for anti-rotavirus IgA antibodies.

Whole blood samples were collected from a subset of 800 subjects on the day of Dose 2 of HRV vaccine or placebo at Visit 2 (1 ml of whole blood to test for anti-rotavirus IgA antibodies), two months after Dose 2 of HRV vaccine or placebo at Visit 3 (3 ml of whole blood to test for anti-rotavirus IgA antibodies and antibodies to concomitant DTPw-HB+Hib vaccination and OPV) and at the end of the first efficacy follow-up period (3 ml of whole blood to test for anti-rotavirus IgA antibodies and antibodies to concomitant DTPw-HB+Hib vaccination and OPV).

A minimum of 1 ml of whole blood was collected from all other subjects at the end of the first efficacy follow-up period to test for anti-rotavirus IgA antibodies.

For subjects receiving three doses of HRV vaccine or placebo: Whole blood samples were collected at Visit 1 and on the day of Dose 3 of HRV vaccine or placebo at Visit 3 (1 ml of whole blood to test for anti-rotavirus IgA antibodies only), and two months after Dose 3 of HRV vaccine or placebo at Visit 4 (3 ml of whole blood to test for anti-rotavirus IgA antibodies and antibodies to concomitant DTPw-HB+Hib vaccination and OPV). Antibodies to DTPw-HB+Hib and OPV vaccines were planned to be measured only at Visit 4 but were also measured at Visit 3.

All blood samples were centrifuged, separated locally and shipped to the laboratories where serum analyses were performed. All serum samples were stored at –20°C and the following serological tests were performed.

Serum anti-rotavirus IgA antibody concentrations were measured by ELISA at the Laboratory of Dr. [redacted] Children's Hospital Medical Centre, Cincinnati, USA and expressed in units per milliliter (U/ml) (refer to *Appendix C: Laboratory assays*). The assay cut-off was 20 U/ml. The ELISA test for anti-rotavirus antibodies uses the "sandwich principle". A solid phase enzyme-linked immunoassay technique is used to detect human anti-rotavirus IgA levels in serum. The assay used was based on the assay previously described by Dr. R. Ward and his co-workers ([6]). The limit of detection of the assay was 5.4 U/ml, whereas the limit of quantification (= the lowest concentration that could be reliably measured) was 13.4 U/ml. Therefore, the technical cut-off has been set at 20 U/ml as a theoretically and practically meaningful value.

A seronegative subject for anti-rotavirus IgA antibodies was defined as a subject who had antibody concentration below the assay cut-off value. A seropositive subject for anti-rotavirus IgA antibodies was defined as a subject who had antibody concentration greater than or equal to the assay cut-off value.

A subject initially negative for RV was defined as a subject who was negative for anti-rotavirus IgA antibodies in serum and for RV antigen in a stool sample at a pre-vaccination time point, if both results were available, or negative for at least one of these markers if only one result was available.

Antibodies against antigens contained in concomitantly administered routine DTPw-HB+Hib vaccines and OPV were tested using standard serological assays as specified in Table 8.

Table 8: Serological assays for antibodies to concomitantly administered routine vaccinations

Antibody	Assays Method	Test Kit manufacturer	Assay Cut-off	Assay units	Laboratory
Anti-diphtheria	ELISA([7])	In-house	0.1	IU/ml	[redacted] Lab
Anti-tetanus	ELISA([8])	In-house	0.1	IU/ml	[redacted] Lab
Anti-BPT	ELISA	In-house	15	EL.U/ml	GSK Rix
Anti-HBs	ELISA	In-house	10	mIU/ml	[redacted] Lab
Anti-PRP	ELISA	In-house	0.15	mcg/ml	[redacted] Lab
Anti-poliovirus type 1	Neutralization	In-house	1:8	dilution titer	[redacted] Lab
Anti-poliovirus type 2	Neutralization	In-house	1:8	dilution titer	[redacted] Lab
Anti-poliovirus type 3	Neutralization	In-house	1:8	dilution titer	[redacted] Lab

Notes: IU = Internation Units
EL.U = Elisa Units
mIU = milli International Units
Comments: [redacted] Lab = Laboratory of Dr. [redacted] University of Rochester, USA
GSK Rix = GlaxoSmithKline Biologicals, Rixensart, Belgium

If there was insufficient serum sample volume to perform assays for all antibodies, tests were performed according to the following priority ranking specified in the protocol: anti-rotavirus IgA, anti-PRP, anti-HBs, anti-diphtheria, anti-tetanus, anti-BPT, anti-poliovirus type 1, anti-poliovirus type 2 and anti-poliovirus type 3.

3.14 Data quality assurance

To ensure that study procedures conformed across all study centres, the protocol, eCRFs and safety reporting procedures were reviewed with the investigators and their personnel responsible for the conduct of the study by the GSK Biologicals representatives at the study sites prior to study start.

Adherence to the protocol requirements and verification of data generation accuracy was achieved through monitoring visits to each investigator site. Computer checks and blinded review of subject tabulations were performed to ensure consistency of eCRF completion. All procedures were performed according to methodologies detailed in GSK Biologicals' Standard Operating Procedures.

There were no major findings affecting the outcome of the procedures applied for testing with RotaClone™ during audits of local laboratories conducted by GSK Biologicals. The local laboratory personnel were coached to implement a full Quality System and maintain appropriate documentation.

There were no major findings affecting the outcome of microbiological co-pathogen testing during audits of local laboratories conducted by GSK Biologicals. Supplementary Quality Control checks and appropriate documentation were implemented at the local laboratories.

Independent Audit statement:
This study was subject to two audits by GSK's department of Worldwide Regulatory Compliance-GCP (WRC-GCP). The WRC-GCP conducted routine compliance audits at the Venezuelan study centre (27–28 February, 2002) and the Brazilian study centre (25–26 September, 2002). There were no critical or major observations identified during both audits.

3.15 Statistical methods

Statistical analyses to be performed were planned and described in the study protocol. All performed analyses, including any additional analyses, are detailed in the Project and Study Report Analysis Plans. The Report Analysis Plans were prepared and finalized before the database was frozen for the analysis at the end of the first efficacy follow-up period.

The analyses were performed using SAS 8.2 and Proc StatXact-5 on Windows NT 4.0.

Note: Although all study endpoints are listed, only analyses of data obtained until the end of the first efficacy follow-up period are presented in this report.

3.15.1 Primary endpoint

For the subset of subjects planned to receive two doses of HRV or placebo:

- Occurrence of any RV GE during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period.

3.15.2 Secondary endpoints

Efficacy endpoints

For the subset of subjects planned to receive two doses of HRV or placebo:

- Occurrence of severe RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of RV GE due to virus types heterologous to vaccine strain during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of any and severe pure RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of RV GE in which there is at least one other pathogen during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.
- Occurrence of hospitalization for RV GE during the period starting from two weeks after Dose 2 until the end of the first efficacy follow-up period.

For the subset of subjects who received three doses of HRV or placebo:

- Occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 3 until the end of the first efficacy follow-up period.

For the subset of subjects who participated in the second efficacy follow-up period until maximum age 24 months:

- For the subset of subjects who received two doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.
- For the subset of subjects who received two doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 2 until the end of the second efficacy follow-up period.
- For the subset of subjects who received three doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.
- For the subset of subjects who received three doses of HRV or placebo, occurrence of any and severe RV GE during the period starting from 2 weeks after Dose 3 until the end of the second efficacy follow-up period.

Safety endpoints

- For each type of solicited symptoms, occurrence of the symptom within the 15-day solicited follow-up period after any dose of study vaccine (in a subset after Dose 3).

- Occurrence of unsolicited symptoms within 43 days (Day 0–Day 42) after Dose 1, Dose 2 (in all subjects) and Dose 3 (in a subset), according to World Health Organization (WHO) classification.
- Occurrence of SAEs throughout the entire study period.

Immunogenicity endpoints

For the subset of subjects planned to receive two doses of HRV or placebo:

- Serum anti-rotavirus IgA antibody concentrations at Visit 1 and the end of the first efficacy follow-up period in all subjects and at Visits 2 and 3 in a subset of subjects.
- Proportion of subjects with vaccine take at Visits 2 and 3 in the stool analysis subset.
- Vaccine take and GMCs of RV IgA ELISA calculated in a subset for breast-fed infants compared with formula fed infants for the following 3 categories: 1) whether the infant received no food 1 hour prior to and 30 minutes after Dose 1 or Dose 2 (as reported by the mother); 2) whether the infant received food 1 hour prior to Dose 1 or Dose 2 (as reported by the mother); and 3) whether the infant received food within 30 minutes after Dose 1 or Dose 2.
- Viral shedding in the vaccine groups in the stool analysis subset.

Two months after Dose 2 (at Visit 3) and at Year 1 in a subset of subjects:

- GMC/Ts for anti-PRP, anti-diphtheria, anti-tetanus, anti-BPT, anti-poliovirus types 1, 2 and 3, and anti-HBs antibodies.
- Seroprotection status:
  - ◊ anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
  - ◊ anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-HBs antibody concentrations ≥ 10 mIU/ml
  - ◊ anti-poliovirus type 1 antibody titers ≥ 8
  - ◊ anti-poliovirus type 2 antibody titers ≥ 8
  - ◊ anti-poliovirus type 3 antibody titers ≥ 8
- Seropositivity status:
  - ◊ anti-BPT antibody concentrations ≥ 15 EL.U/ml

For the subset of subjects who received three doses of HRV or placebo:

- Serum anti-rotavirus IgA antibody concentrations at Visits 1, 3 and 4.
- GMC/Ts for anti-PRP, anti-diphtheria, anti-tetanus, anti-BPT, anti-poliovirus types 1, 2 and 3, and anti-HBs antibodies two months after Dose 3.
- Seroprotection status two months after Dose 3:
  - ◊ anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
  - ◊ anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml

  - ◊ anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-HBs antibody concentrations ≥ 10 mIU/ml
  - ◊ anti-poliovirus type 1 antibody titers ≥ 8
  - ◊ anti-poliovirus type 2 antibody titers ≥ 8
  - ◊ anti-poliovirus type 3 antibody titers ≥ 8
- Seropositivity status two months after Dose 3:
  - ◊ anti-BPT antibody concentrations ≥ 15 EL.U/ml
- Viral shedding in the vaccine groups on the day of and on Day 7 after Dose 3.

3.15.3 Determination of sample size

The target sample size was planned at 2640 enrolled subjects to reach 2360 subjects (590 per group) in the ATP cohort for efficacy analysis to evaluate the primary objective. However, the target sample size was reduced to 2276 subjects in the amendment 3 dated May 3, 2002 because of difficulty in enrolling eligible subjects for participation in the study. Amendment 3 dated May 3, 2002 also planned that 200 of the 2276 subjects were to receive a third dose of HRV vaccine or placebo.

Thus, the final eligible sample size for analysis of the primary efficacy objective was to be 2076 eligible subjects (460 evaluable subjects per group) to receive two doses of HRV vaccine or placebo for the analysis of the primary objective.

The anticipated attack rate in the placebo for any RV GE was 12%. However, with the observed attack rate of 10.8% for any RV GE in the placebo, and assuming vaccine efficacy of 70%, sample size of 2076 eligible subjects provided more than 82% power that the lower limit (LL) of the 95% Confidence Intervals (CIs) for efficacy against any RV GE during the first efficacy follow-up period is above 30% (see Table 9). With this sample size of 2076 subjects and the observed attack rate, the study was still sufficiently powered to evaluate the study objectives and draw conclusions.

The sample size justification was done by calculating the power using different efficacy estimates for a vaccine group and for a range of attack rates of any RV GE (primary endpoint) and severe RV GE (secondary endpoint) in the placebo as shown in Table 9. Power was higher for the evaluation of efficacy on pooled HRV.

Table 9: Power to get an exact 95% CI for the vaccine efficacy for a vaccine group above a specific cut-off (N = 460 subjects by group, power based on 1.000 simulations using Proc StatXact) (Refer to Appendix B for mathematical details)

% of subjects reporting RV GE in the placebo group from two weeks after Dose 2 until the end of the efficacy follow-up period following vaccination	**% of subjects reporting RV GE in the vaccine group from two weeks after Dose 2 until the end of the efficacy follow-up period following vaccination**	**Efficacy (%)**	**Cut-off (LL of 95% CI for vaccine efficacy)**			
			0%	10%	20%	30%
Any RV GE			**Power that the LL is above each cut-off**			
12%*	3.6%	70%	99.7%	99.2%	97%	88.9%
12%*	4.8%	60%	96.8%	92.0%	81.8%	58.1%
12%*	6 %	50%	84.1%	71.1%	48.8%	26.7%
10%	3%	70%	98.8%	97.4%	92.4%	82.2%
10%	4%	60%	93.5%	84.8%	71.4%	51.2%
10%	5%	50%	77.4%	61.7%	41.4%	20.5%
Severe RV GE						
4%*	0.8%	80%	89%	84%	76%	
4%*	1%	75%	80%	74%	63%	
4%*	1.2%	70%	72%	62%	50%	
3%	0.6%	80%	75%	68%	61%	
3%	0.75%	75%	63%	52%	44%	
3%	0.9%	70%	56%	45%	37%	

Comment: *anticipated incidence rate

The analysis looked at the pooled vaccine groups *versus* placebo and each vaccine group *versus* placebo.

In order to control the risk of falsely concluding below 5%, the primary objective was addressed using a hierarchical testing. Pooled HRV vaccine group was first tested and, only if efficacy was demonstrated, the vaccine with a viral concentration of $10^{5.8}$ ffu was tested. Likewise, only if efficacy of vaccine with a viral concentration of $10^{5.8}$ ffu was demonstrated, the vaccine with a viral concentration of $10^{5.2}$ ffu was tested. Likewise, only if efficacy of vaccine with a viral concentration of $10^{5.2}$ ffu was demonstrated, the vaccine with a viral concentration of $10^{4.7}$ ffu was tested. Efficacy was established if the percentage of subjects with RV GE during the period starting from 2 weeks after Dose 2 of HRV vaccine or placebo until the end of the efficacy follow-up period following vaccination in the HRV vaccine group was statistically significantly lower than in the placebo group (two-sided Fisher Exact test: $p < 0.05$).

It should be noted that only 121 subjects of the planned 200 received a third dose of HRV vaccine or placebo. Therefore, the final eligible sample size for analysis of the primary objective was 2155 subjects.

The size of the subset to be followed during the second efficacy follow-up period was based on the assumption that the attack rate of any RV GE would be 12% in the placebo group. Assuming 60% vaccine efficacy, a subset of 200 subjects in each group was estimated to provide 88% and 67% power to detect a statistically significant vaccine effect with the pooled HRV vaccine group and each vaccine group, respectively (2 sided Fisher's exact test, alpha = 5%, no adjustment for multiplicity). Thus, a subset of approximately 1000 subjects who had not completed the study as of October 31, 2002 participated in the second efficacy follow-up period until maximum 24 months of age.

The size of the subset to assess the immunogenicity of the concomitant routine vaccinations and OPV was based on the assumption that seroprotection rates would be between 90% and 98% (for anti-diphtheria, anti-tetanus, anti-PRP, anti-HBs and anti-poliovirus types 1, 2 and 3 antibodies) and anti-BPT Geometric Mean Concentration (GMC) would be 27.3 EL.U/ml (with a standard deviation of 0.332) (reference study: DTPw-HBV-Hib-003), and assuming that the rates/GMC/GMT would be the same in the vaccine and placebo groups. A subset of 175 evaluable subjects per group was estimated to provide 80% global power to show that all the 95% CI on the decrease in seroprotection rates in the HRV vaccine group as compared to the placebo group are below 15% and that the 95% CIs on the fold decrease in anti-BPT GMCs in the HRV vaccine group as compared to the placebo group is below 1.5 (power based on 1000 simulations with proc StatXact for the difference in seroprotection rates and using Nquery for the ratio of anti-BPT GMCs, one sided equivalence test, alpha = 2.5%). Allowing for up to 12% of subjects who may not be evaluable for the immunogenicity analysis, blood samples were taken from approximately 200 subjects per group to assess immunogenicity of concomitant routine vaccinations and OPV. This power calculation was done for analyses at approximately 6 months after completion of the routine three-dose primary vaccination course (at the end of the first efficacy follow-up period). However, immunogenicity of routine vaccinations was also analysed at two months after Dose 2 of HRV vaccine or placebo (which corresponds to Dose 2 of routine vaccinations).

An amendment dated May 3, 2002 allowed administration of a third dose of the HRV vaccine or placebo to a subset of infants following the interim immunogenicity analysis performed in March 2002. A subset of approximately 200 subjects from Brazil and Venezuela who had not completed Visit 3 at the time of the amendment were planned to receive a third dose of HRV vaccine or placebo at Visit 3. The amendment was not approved in Venezuela, and therefore only 121 subjects from Brazil were part of the subset receiving a third dose HRV vaccine or placebo. Only descriptive analyses were performed on the data from the subset receiving three doses of HRV vaccine or placebo.

3.15.4 Study cohorts/data sets analyzed

The following subject cohorts were evaluated:

Total vaccinated cohort
The total vaccinated cohort included all subjects with at least one study vaccine administration documented:

- Safety analysis based on the total vaccinated cohort included all vaccinated subjects.
- Immunogenicity analysis based on the total vaccinated cohort included all vaccinated subjects for whom immunogenicity data were available.
- Efficacy analysis based on the total vaccinated cohort for the subset of subjects planned to receive two doses of HRV or placebo included all vaccinated subjects for whom efficacy follow-up data were available. Efficacy follow-up was derived from any contact
    - beyond 2 weeks after the second dose of HRV vaccine or placebo for the first efficacy follow-up period.
- Efficacy analysis based on the total vaccinated cohort for the subset receiving three doses of HRV vaccine or placebo included all vaccinated subjects for whom efficacy follow-up data were available. Efficacy follow-up was derived from any contact
    - beyond 2 weeks after the third dose of HRV vaccine or placebo for the first efficacy follow-up period.

ATP cohort for safety analysis
The ATP cohort for safety analysis included all subjects:

- who had received at least one dose of HRV vaccine or placebo according to the randomization list,
- for whom the randomization code had not been broken by the investigator,
- who had not received a vaccine forbidden by or not specified in the protocol,

- for whom the HRV vaccine or placebo was administered according to the protocol, (Note: subjects who regurgitated within 30 minutes after vaccination were eliminated for this reason)
- who had not received a replacement vial, except if the appropriate vaccine was administered in "double-blind replacement",
- who were negative for RV antigen on the day of Dose 1 of HRV vaccine or placebo.

ATP cohort for immunogenicity analysis
The ATP cohort for immunogenicity analysis included all subjects from the ATP safety cohort:
- who had not received medication forbidden by the protocol,
- whose underlying medical condition was not forbidden by the protocol,
- with no protocol violation of demographics (unknown age at study entry or outside protocol defined age-interval),
- who complied with vaccination schedule,
- who complied with blood sampling schedule,
- who had no RV other than vaccine strain in stool samples collected during the vaccination period (from Visit 1 to Visit 3),
- who had no concomitant infection unrelated to the vaccine which may influence the immune response.
- for whom post results (for anti-rotavirus IgA antibodies or for stool) were available at least one post-vaccination timepoint up to the end of the first efficacy follow-up period.

ATP cohort for efficacy analysis
The ATP cohort for efficacy analysis for the first efficacy follow-up period included all subjects from the ATP safety cohort:
- who received 2 doses of HRV vaccine or placebo,
- who had no RV other than vaccine strain in stool samples collected between the day Dose 1 of HRV vaccine or placebo was administered and 2 weeks after Dose 2 of HRV vaccine or placebo was administered,
- who had entered into the surveillance period: had follow-up beyond 2 weeks after Dose 2 of HRV vaccine or placebo.

Datasets analyzed
For the subset planned to receive two doses of HRV vaccine or placebo
The total vaccinated cohort was used for the primary analysis of safety. The analysis on the ATP cohort for safety was to be performed only if more than 5% of the enrolled subjects were excluded from the ATP safety cohort.

Analysis of efficacy during the first efficacy follow-up period was performed on the ATP cohort (primary analysis) and the total vaccinated cohort.

The ATP immunogenicity cohort was used for the primary analysis of immunogenicity. An analysis of immunogenicity based on the total vaccinated cohort was to be performed only if more than 5% of the enrolled subjects were excluded from the ATP immunogenicity cohort. In such a case, the analysis on the total vaccinated cohort evaluated whether exclusion from the ATP cohort had biased the results.

Subjects excluded from the ATP cohorts were identified before data analysis after a review of the individual subject data blinded to group allocation.

For the subset receiving three doses of HRV vaccine or placebo
The analyses of safety, efficacy and immunogenicity were performed only on the total vaccinated cohort.

3.15.5 Analysis of demographics

3.15.5.1 For the subset planned to receive two doses of HRV vaccine or placebo

Demographic characteristics (age, height and weight descriptive statistics, and gender and race distribution) at Visit 1 were tabulated by group for the ATP cohort for efficacy analysis, the ATP cohort for immunogenicity analysis and the total vaccinated cohort. For the total vaccinated cohort, this analysis was also done by country.

The height and weight increases at each visit were tabulated for the total vaccinated cohort.

Summary of feeding criteria on the day of each study vaccination was presented by group for the ATP cohort for immunogenicity analysis.

The percentages of subjects who received OPV at birth were tabulated for the ATP cohort for immunogenicity analysis.

3.15.5.2 For the subset receiving three doses of HRV vaccine or placebo

Demographic characteristics (age, height and weight descriptive statistics, and gender and race distribution) at Visit 1 were tabulated by group for subjects included in the total vaccinated cohort.

The height and weight increases at each visit were tabulated for the total vaccinated cohort.

Summary of feeding criteria on the day of each study vaccination was presented by group for the total vaccinated cohort.

3.15.6 Analysis of efficacy

3.15.6.1 Efficacy during first efficacy follow-up period for the subset planned to receive two doses of HRV vaccine or placebo

The first efficacy follow-up period started from two weeks after Dose 2 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age).

All calculations were done for each study group and for pooled HRV vaccine groups.

The duration of the efficacy follow-up period was tabulated by group.

A global overview of the number of GE episodes of any etiology (RV or not) and RV GE episodes during the first efficacy follow-up period was provided by severity. A summary of RV GE episodes reported during the first efficacy follow-up period by type was provided.

The percentages of subjects with any and severe RV GE (all RV types, by RV type and by country) and percentages of subjects hospitalized due to RV GE during the first efficacy follow-up period were calculated with their 95% CI. Two-sided Fisher's exact test (significance level of α=0.05) was used to compare these percentages between vaccine groups and placebo.

Proportion of pure RV GE and mixed RV GE cases was evaluated by calculating the proportion of RV GE episodes with concurrent presence of at least one other pathogen.

The percentages of subjects reporting at least one RV GE episode during the first efficacy follow-up period according to the serological status for IgA antibodies at two months after Dose 2 of HRV vaccine or placebo were computed.

Efficacy of the HRV vaccine during the first efficacy follow-up period was calculated with its 95% CI against

- any and severe RV GE
- any and severe RV GE by RV type
- hospitalization due to RV GE

Vaccine efficacy, with 95% CI, against any and severe RV GE was also calculated by country.

Vaccine efficacy was defined as the percent reduction in the frequency of the considered endpoint in vaccinated subjects compared with those subjects who received placebo.

The vaccine efficacy was calculated using the formula: 1 – RR = 1 – (ARV/ARU)

RR = relative risk = ARV/ARU

- ARU = disease attack rate in unvaccinated population (estimated from the placebo group) = nu/Nu = number of subjects reporting at least one RV GE episode / total number of subjects in the placebo (control) group.
- ARV = disease attack rate in vaccinated group = nv/Nv = number of subjects reporting at least one RV GE episode / total number of subjects in the HRV vaccine group.

The 95% CIs for vaccine efficacy were derived using a conditional to cases approach (refer to *Appendix B: Mathematical details about the computation of the 95% CI for vaccine efficacy*).

To check the robustness with respect to the statistical analysis, vaccine efficacy against the primary endpoint (occurrence of any RV GE from 2 weeks after Dose 2 of HRV vaccine or placebo until the end of the efficacy follow-up period) and its 95% CI were also estimated by the Cox proportional-hazard model including the group effect as regressor. The Kaplan Meier survival curves were generated to analyze the time from 2 weeks after Dose 2 of HRV vaccine or placebo to the onset of RV GE. The time was censored at the last contact in the first efficacy follow-up period.

In addition, person-year rates of any and severe RV GE (all RV types and by RV type), hospitalization due to RV GE and any and severe RV GE by country within each group were assessed using a loglinear Poisson model.

In order to control the risk of falsely concluding below 5%, the primary objective (prevention of any RV GE from 2 weeks after Dose 2 of HRV vaccine or placebo until the end of the efficacy follow-up period) was assessed using a hierarchical testing. Pooled HRV vaccine group was tested first and, only if efficacy was demonstrated, Group $10^{5.8}$ ffu HRV was tested. Likewise, only if efficacy of Group $10^{5.8}$ ffu HRV was demonstrated, Group $10^{5.2}$ ffu HRV was tested. Likewise, only if efficacy of Group $10^{5.2}$ ffu HRV was demonstrated, Group $10^{4.7}$ ffu HRV was tested. Efficacy was established if the percentage of subjects with RV GE during the period starting from 2 weeks after Dose 2 of HRV vaccine or placebo until the end of the efficacy follow-up period following vaccination in the HRV vaccine group was statistically significantly lower than in the placebo group (two-sided Fisher's Exact test: $p < 0.05$).

In order to have a first look at the effectiviness of the vaccine from the first dose onwards, occurrence of RV GE episodes from Day of Dose1 till Day 14 of Dose 2 and occurrence of RV GE episodes from Day of Dose1 till the end of the first efficacy follow-up period were evaluated. These analyses were performed only on the total vaccinated cohort. The percentages of subjects with any and severe RV GE from Day of Dose1 till Day 14 of Dose 2 and from Day of Dose1 till the end of the first efficacy follow-up period were calculated by groups and for pooled HRV groups, with their 95% CI. Two-sided Fisher's exact test (significance level of α=0.05) was used to compare rates between vaccine groups and placebo for the period starting from Day of Dose1 till the end of the first efficacy follow-up period. Vaccine efficacy, with 95% CI, was calculated against any and severe RV GE occurring from Day of Dose1 till Day 14 of Dose 2 and against any and severe RV GE occurring from Day of Dose1 till the end of the first efficacy follow-up period.

3.15.6.2 Exploratory efficacy during the first efficacy follow-up period for the subset receiving three doses of HRV vaccine or placebo

The first efficacy follow-up period started from two weeks after Dose 3 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age).

The percentages of subjects with RV GE (any and severe intensity) from two weeks after Dose 3 of HRV vaccine or placebo until the end of the first efficacy follow-up period were calculated with their exact 95% CI.

3.15.7 Analysis of safety

Solicited symptoms were recorded during the 15-day (Day 0 to Day 14) solicited follow-up period after each study vaccination. Unsolicited symptoms were recorded during the 43-day (Day 0 to Day 42) follow-up period after each study vaccination. SAEs were recorded during the entire study period.

3.15.7.1 Reactogenicity of two doses of HRV vaccine and placebo

The following calculations were performed for each study group and for pooled HRV vaccine groups:

The percentages of doses and of subjects reporting at least one AE (solicited or unsolicited) during the solicited follow-up period were computed, along with exact 95% CI. The same calculations were done for symptoms rated as grade "3" in intensity and for symptoms assessed as related to vaccination. These calculations were also done by country.

The percentages of doses and of subjects reporting specific solicited symptoms were calculated, with exact 95% CI, over the solicited follow-up period (Day 0 to Day 14). The same calculations were done for solicited symptoms rated as grade "2 or 3" in intensity, rated as grade "3" in intensity and for solicited symptoms assessed as related to vaccination. These calculations were also done by country.

Pair-wise differences among the three HRV vaccine groups and between the pooled HRV vaccine group and the placebo group were explored using the two-sided Fisher's exact test for the endpoints mentioned below. Statistically significant differences (p-value < 0.05) should be interpreted cautiously since, due to the number of endpoints, the differences observed in this study are likely to occur by chance alone.

- percentage of subjects reporting each individual solicited symptom within the 15-day (Days 0 to Day 14) follow-up period after any dose of HRV vaccine or placebo.
- percentage of subjects reporting each individual solicited symptom within the 8-day (Days 0 to Day 7) follow-up period after any dose of HRV vaccine or placebo.
- percentage of subjects reporting each individual grade "3" solicited symptom within the 8-day (Days 0 to Day 7) follow-up period after any dose of HRV vaccine or placebo.
- percentage of subjects reporting each individual grade "2 or 3" solicited symptoms within the 8-day (Days 0 to Day 7) follow-up period after any dose of HRV vaccine or placebo.
- percentage of subjects reporting each individual solicited symptoms assessed as related to vaccination within the 8-day (Days 0 to Day 7) follow-up period after any dose of HRV vaccine or placebo.

Prevalence of diarrhea, vomiting and fever by day during the solicited follow-up period were displayed graphically, by group. Prevalence is the percentage of subjects who reported the event at a certain (fixed) time point among doses administered.

Descriptive statistics for duration of diarrhea, vomiting and fever during the solicited follow-up period by dose and for overall doses were tabulated. Missing value at a specific day was considered as absence of the symptom on that day.

The verbatim reports of unsolicited symptoms were coded by use of the WHO's Dictionary for Adverse Reaction Terminology; every verbatim term, as stated by the reporter, was matched to the appropriate WHO Preferred Term associated to the symptom. The percentage of subjects and of doses reporting unsolicited symptoms classified by WHO body system/WHO Preferred Terms within 43 days (Day 0–Day 42) after vaccination were tabulated, with exact 95% CI. Similar tabulations were also done for unsolicited symptoms rated as grade "3" in intensity and those assessed as related to vaccination. These tabulations were also done by country.

The percentage (with exact 95 % CI) of subjects and doses reporting gastrointestinal symptoms (WHO code 600) including those graded "3" in intensity and those considered to be related to vaccination, within 43 days (Day 0–Day 42) after vaccination were tabulated.

The percentages of subjects who took at least one concomitant medication during the solicited follow-up period (Day 0–Day 14 after vaccination) were tabulated by type of medication. The prevalence of subjects who took antipyretics from Day 0 to Day 42 after vaccination was displayed graphically.

The number of SAEs occurring until the end of the first efficacy follow-up period were reported. SAEs assessed as possibly related to vaccination, SAEs with fatal outcome and IS cases were described. There may be minor discrepancies in the details of the SAEs included in the clinical narratives compared with the safety tabulations. This is because the data came from two different databases using different classifications [WHO/ Medical Dictionary for Regulatory Activities (MedDRA)] and was collected at different points in time. However, it was considered that these differences, if any were minor in nature and do not change the overall clinical significance or understanding of the SAE.

3.15.7.2 Reactogenicity of HRV vaccine and placebo in the subset receiving three doses of HRV vaccine or placebo

All descriptive analysis described in Section 3.15.7.1, except duration and prevalence of diarrhea, vomiting and fever during the solicited follow-up period and incidence of unsolicited gastrointestinal symptoms, were performed on reactogenicity and safety data obtained in the subset receiving three doses of HRV vaccine or placebo.

3.15.8 Analysis of immunogenicity

3.15.8.1 Immunogenicity of the HRV vaccine for the subset planned to receive two doses of HRV vaccine or placebo

GMCs and seropositivity rates to anti-rotavirus IgA antibodies were calculated with their 95% CI for each group, at each time point that blood samples were available. GMCs (expressed in U/ml) were computed by taking the anti-log of the mean of the log titer transformations. Antibody concentrations below the cut-off were given an arbitrary value of half the cut-off for the purpose of GMC calculation.

A subject who had seroconverted for anti-rotavirus IgA antibodies at a post-vaccination sampling timepoint was defined as a subject with appearance of anti-rotavirus IgA antibody concentration ≥ 20 U/ml in subjects initially (i.e. prior to the first dose of HRV vaccine or placebo) negative for RV. The seroconversion rate was the seropositivity rate at the post-vaccination sampling timepoint in subjects initially negative for RV (for the ATP cohort, at post Dose 1 and post Dose 2 time point, seroconversion rate = seropositivity rate).

Seroconversion rate on combined doses was also calculated, using the rule describe below:

Rule for calculating seroconversion on combined doses 1 and 2, at Visit 3:

Seroconversion in the blood sample taken after Dose 2 at Visit 3	Seroconversion in the blood sample taken after Dose 1 (at Visit 2)	Estimate seroconversion rate for the blood sample taken at Visit 3 (i.e., based on the result of column 1 and 2)
Yes	Yes, No or Unknown	Seroconversion
No	Yes	Seroconversion
No	No	No seroconversion
No	Unknown	No seroconversion
Unknown	Yes	Seroconversion
Unknown	No	NC
Unknown	Unknown	NC

NC = Not considered in the calculation

The distribution of anti-rotavirus IgA antibody concentrations at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period were displayed using reverse cumulative curves.

In order to compare antibody concentrations induced by the vaccine across the studies, and also to compare with antibody concentrations induced by natural RV infection, anti-rotavirus IgA antibody GMCs were also calculated on the subjects who had seroconverted after vaccination or natural infection.

Stool analysis subset:

The stool analysis subset consisted of subjects with at least one available result for stools collected at pre-determined timepoints.

GMCs and seropositivity rates to anti-rotavirus IgA antibodies were calculated with their 95% CI for each group, at each time point that blood samples were available. GMCs were computed by taking the anti-log of the mean of the log titer transformations. Antibody concentrations below the cut-off were given an arbitrary value of half the cut-off for the purpose of GMC calculation.

RV shedding was evaluated by calculating the percentage of subjects with presence of RV in stool samples collected at Day 0 and Day 7 of each HRV vaccine or placebo dose and after combined doses.

The percentage of subjects with vaccine take after each HRV vaccine or placebo dose and after combined doses were calculated with their exact 95% CI. Vaccine take rates were defined as the percentage of subjects with appearance of serum anti-rotavirus IgA antibody concentration ≥ 20 U/ml or vaccine virus in any stool sample collected during the specified period in subjects initially negative for rotavirus. In this study, vaccine take was calculated only for the stool analysis subset.

Vaccine take rates were calculated using the rule described below:

Rule for estimating vaccine take after Dose 1:

Seroconversion in the blood sample taken after Dose 1 (at Visit 2)	Vaccine virus in any stools collected from Dose 1 to the blood sample taken at Visit 2	Estimate vaccine take for the blood sample taken at Visit 2 (i.e., based on the result of column 1 and 2)
Yes	Yes, No or Unknown	**Vaccine take**
No	Yes	**Vaccine take**
No	No	No vaccine take
No	Unknown	No vaccine take
Unknown	Yes	**Vaccine take**
Unknown	No	NC
Unknown	Unknown	NC

NC = Not considered in the calculation

Rule for estimating vaccine take after Dose 2:

Seroconversion in the blood sample taken after Dose 2 at Visit 3	Vaccine virus in any stool collected from Dose 2 to the blood sample taken at Visit 3	Estimate vaccine take for the blood sample taken at Visit 3 (i.e., based on the result of column 1 and 2)
Yes	Yes, No or Unknown	**Vaccine take**
No	Yes	**Vaccine take**
No	No	No vaccine take
No	Unknown	No vaccine take
Unknown	Yes	**Vaccine take**
Unknown	No	NC
Unknown	Unknown	NC

NC = Not considered in the calculation

Vaccine take on combined Doses 1 and 2, at Visit 3:

Seroconversion in the blood sample taken after Dose 2 at Visit 3	Vaccine virus in any stool collected from Dose 1 to the blood sample taken at Visit 3 or seroconversion in the blood sample taken after Dose 1 (at Visit 2)	Estimate vaccine take for the blood sample taken at Visit 3 (i.e., based on the result of column 1 and 2)
Yes	Yes, No or Unknown	**Vaccine take**
No	Yes	**Vaccine take**
No	No	No vaccine take
No	Unknown	No vaccine take
Unknown	Yes	**Vaccine take**
Unknown	No	NC
Unknown	Unknown	NC

NC = Not considered in the calculation

Differences between each HRV vaccine group and placebo were evaluated with respect to vaccine take on combined doses at two months after Dose 2 (at Visit 3) by calculating the asymptotic standardized two-sided 95% CI for difference in vaccine take between each HRV vaccine group and the placebo group.

Impact of feeding on immunogenicity of the HRV vaccine

The impact of feeding on the vaccine take at two months after Dose 2 of HRV vaccine or placebo, on combined doses, was explored using a logistic regression. Only the HRV vaccinated subjects were accounted in the regression. A stepwise procedure was used to identify the statistically significant factors among those described below.

Category	Dose
Only breast-fed	at both doses at the first dose only at the second dose only for none of the doses
Breast-fed + formula-fed	at both doses at the first dose only at the second dose only for none of the doses
Fed within 1 hour before vaccination	at both doses at the first dose only at the second dose only for none of the doses
Fed within 30 minutes after vaccination	at both doses at the first dose only at the second dose only for none of the doses
Group	HRV $10^{4.7}$ HRV $10^{5.2}$ HRV $10^{5.8}$

A 2-sided p-value less than 0.10 for the factor effect was used to retain or discard a factor as being not significant.

Vaccine take on combined doses was to be calculated according to the findings of the logistic regression.

3.15.8.2 Immunogenicity of routine DTPw-HBV+Hib and OPV vaccines for the subset receiving two doses of HRV vaccine or placebo

Analysis of immunogenicity of routine vaccinations for the ATP cohort was performed on the subset of subjects who had documented receipt of at least two doses of routine vaccines between Visit 1 and before the end of the first efficacy follow-up period.

The following calculations were done for each study group and for pooled HRV vaccine groups:

GMC/Ts and seropositivity/seroprotection rates for anti-diphtheria, anti-tetanus, anti-BPT, anti-HBs, anti-PRP, anti-poliovirus types 1, 2 and 3 antibodies were calculated with their 95% CI. GMC/Ts were computed by taking the anti-log of the mean of the log titer transformations. Antibody concentrations below the cut-off were given an arbitrary value of half the cut-off for the purpose of GMC/T calculation.

Differences between the pooled HRV vaccine group/each HRV vaccine group and placebo group with respect to immune response to concomitant vaccination at two months after Dose 2 of HRV vaccine or placebo and at the end of first efficacy follow up period were evaluated using:

- asymptotic standardized two-sided 95% CI for the differences in seroprotection or seropositivity rates between groups.
- two-sided 95% CI for the ratio of GMC/Ts between groups. This calculation was performed using a one-way ANOVA model on the logarithm10 transformation of the concentrations using the vaccine group as only covariate.

These inferential analyses were exploratory and clinical limits for non-inferiority were not pre-defined.

The distribution of antibody concentrations/titers two months after Dose 2 of HRV or placebo and at the end of the first efficacy follow-up period were displayed using reverse cumulative curves.

3.15.8.3 Immunogenicity analysis for the subset receiving three doses of HRV vaccine or placebo

At each time point that antibodies to a given antigen (HRV or placebo, DTPw-HB+Hib and OPV) were measured, GMC/Ts and seroconversion/seroprotection/seropositivity rates were calculated with their 95% CI for each group.

The distribution of anti-rotavirus IgA antibody concentrations at two months after Dose 2 of HRV vaccine or placebo and at two months after Dose 3 of HRV vaccine or placebo were displayed using reverse cumulative curves.

Anti-rotavirus IgA antibody GMCs were also calculated on the subjects who had seroconverted after vaccination or natural infection.

RV shedding was evaluated by calculating the percentage of subjects with presence of RV in stool samples collected at pre-determined timepoints after vaccination.

The distribution of antibody levels induced by routine vaccinations at two months after Dose 3 of HRV vaccine or placebo were displayed using reverse cumulative curves.

3.16 Interim analyses

Five interim analyses were performed as planned in the protocol. Unblinding and access to the individual treatment code during each interim analysis was restricted to the statistician and the database administrator. No study report was written for the interim analyses and dissemination of results of the interim analyses was strictly controlled. The results of all the interim analyses mentioned below are available ([9]).

- In March 2002, a planned interim analysis was performed to provide early information for dose selection. This analysis presented a descriptive summary of immunogenicity and reactogenicity for the study vaccine and immunogenicity data for routine vaccinations. The results of this interim analysis were consistent with the results presented in this study report.

- In August 2002, a planned interim analysis on efficacy against any and severe RV GE, overall and by type was performed to obtain preliminary efficacy data. This interim efficacy analysis was performed when the number of RV GE cases from two weeks after Dose 2 of HRV vaccine or placebo reached 70. This allowed demonstration of efficacy (with LL of 95% CI >0) with 75% power based on the following conservative assumption: vaccine efficacy (for pooled HRV vaccine groups) against any RV GE is 50%, with an attack rate of 6% in the placebo group. No adjustment on the alpha or the power were applied for the final analyses of efficacy. The results of this interim analysis were consistent with the results presented in this study report.

- In February 2003, a planned interim analysis on data after Dose 3 of HRV vaccine or placebo was performed. This analysis presented a descriptive summary of immunogenicity for the study vaccines. The results of this interim analysis were consistent with the results presented in this study report.

- In September 2003, analyses for transplacental anti-rotavirus IgG antibodies and transplacental anti-rotavirus neutralizing antibodies in study rota-008 (annex protocol implemented in a subset from study rota-006) were performed. The results of the analyses are presented in the report "The Interference of Transplacental Antibodies on Response to GSK Biologicals' Human Rotavirus Vaccine: Rota-004, Rota-008 and Rota-014".

- In October 2003, a planned interim analysis on efficacy against any and severe RV GE at the end of the second efficacy follow-up period in Mexico was performed to obtain early efficacy data during the second efficacy follow-up period. No adjustment on the alpha or the power will be applied for the final analyses of efficacy. A separate annex report will present efficacy and safety data during the second efficacy follow-up period from all subjects (from Brazil, Mexico and Venezuela) who were followed until maximum age 24 months.

The results of interim analyses were presented at scientific conferences and to the authorities, as required, however unblinding at the level of individual data was restricted to the statistician and the database administrator.

3.17 Annex analyses

A separate annex report will present efficacy and safety data during the second efficacy follow-up period as well as efficacy over two consecutive follow-up periods from all subjects who were followed until maximum age 24 months.

A separate report will present all data obtained during study rota-008.

A separate report will present all data on characterisation of the immune response of the HRV vaccine (maternal antibodies and neutralizing antibodies) from subsets of subjects enrolled in study rota-006.

A separate report will present all data obtained during the site-specific evaluation of fecal RV IgA immune response in a subset of subjects enrolled in study rota-006 in Venezuela.

3.18 Changes in conduct of the study/planned analyses

The following changes were made to the planned analyses:

- The total vaccinated cohort was used for the analyses instead of the total cohort.
- If RV was detected in stool samples collected at pre-determined timepoints from subjects in the placebo group, G type was determined *post-priori* by RT-PCR at GSK Biologicals, Rixensart, Belgium.
- An increase in the incidence of specific symptoms after vaccine administration (pooled HRV vaccine groups) as compared to placebo, was explored using a two-sided Fisher's exact test (with an alpha of 5%) instead of a one-sided Fisher's exact test (with an alpha of 5%) to standardize with future studies.

- The standardized asymptotic method was used for inference on the difference of two proportions instead of exact method by Santner and Snell specified in the protocol. The type 1 error and the power were not impaired due to this change.
- Vaccine efficacy estimates against pure and mixed RV GE was not calculated since no concurrent pathogen was identified in the majority of RV GE episodes.
- Since none of the assessed factors (feeding criteria) had a significant effect in the logistic regression, the vaccine take by feeding criteria were not calculated.
- For the subjects receiving three doses of HRV vaccine or placebo, serum levels of antibodies to routine vaccinations were measured also at two months after Dose 2 of HRV vaccine or placebo, although not planned in the protocol.

4 Study population planned to receive two doses of HRV vaccine or placebo

4.1 Study dates

The study began on May 25, 2001 (first subject, first visit). The data lock point for this final analysis was April 24, 2003 (the day on which the last subject completed the study visit at the end of the first efficacy follow-up period).

A subset of approximately 1000 subjects was followed for efficacy during the second efficacy follow-up period (until maximum age 24 months). The second efficacy follow-up period in Mexico ended in June 2003 (after the end of the 2003 RV season). The second efficacy follow-up period in Brazil and Venezuela ended in October 2003.

4.2 Subject eligibility and attrition from study

4.2.1 Number and distribution of subjects

A total of 2155 subjects were enrolled in the study to receive two doses of HRV vaccine or placebo after checking of inclusion/exclusion criteria. The number of subjects at each study centre is presented in Table 10.

Table 10: The number of subjects enrolled at each study centre by group (total vaccinated cohort)

Country	Centre	Group					
		HRV $10^{4.7}$	HRV $10^{5.2}$	HRV $10^{5.8}$	Placebo	All	
		n	n	n	n	n	%
Brazil	[redacted]	194	196	194	194	778	36.1
Mexico	[redacted]	101	101	102	101	405	18.8
Venezuela	[redacted]	243	243	244	242	972	45.1
All	All	538	540	540	537	2155	100

Notes: Centre = GSK assigned centre number
n = number of subjects enrolled in each group or in total for a given centre or for all centres
% = percentage of subjects enrolled for a given centre or for all centres
All = sum of all subjects in each group, in total for all groups or in total for all centres

4.2.2 Study completion and drop out

A total of 151 subjects dropped out of the study until the end of the first efficacy follow-up period for reasons detailed in Table 11.

Table 11: Counts of subjects enrolled, completed, dropped out and reason for drop out until the end of the first efficacy follow-up period (total vaccinated cohort)

	Groups				Total
	HRV $10^{4.7}$	HRV $10^{5.2}$	HRV $10^{5.8}$	Placebo	
Number of subjects enrolled	538	540	540	537	2155
Number of subjects completed	500	499	499	506	2004
Number of subjects dropped out	38	41	41	31	151
Reasons for drop-out:					
SAE	1	0	1	1	3
Non-serious AE	0	2	2	2	6
Protocol violation	0	0	1	1	2
Consent withdrawal (not due to an adverse event)	13	21	9	9	52
Migrated/moved from study area	21	17	24	18	80
Lost to follow-up (subjects with incomplete vaccination course)	1	0	1	0	2
Lost to follow-up (subjects with complete vaccination course)	1	0	0	0	1
Others	1	1	3	0	5

Notes: Enrolled = number of subjects who were enrolled in the study
Completed = number of subjects who completed Visit 4 at the end of the first efficacy follow-up period
Dropped out = number of subjects who did not come at Visit 4 at the end of the first efficacy follow-up period

Most of the subjects dropped either because of consent withdrawal or because they moved from the study area.

Three subjects died due to unrelated SAEs. Refer to Section 6.2.6.2 for details on SAEs with a fatal outcome.

Details of the non-serious adverse events that led to six drop outs are as follows:

Drop outs due to non-serious AEs assessed as related to vaccination:

- One subject was withdrawn after Dose 1 of HRV vaccine or placebo after experiencing an allergic reaction (grade 2 intensity) starting on the day of Dose 1. The subject recovered after two weeks. The subject had received DTPw-HB+Hib vaccine concomitantly with the study vaccine. It was not specified whether the study vaccine or the routine concomitant vaccine caused the allergic reaction.

Drop outs due to non-serious AEs assessed as not related to vaccination:

- One subject had a history of gastrointestinal reflux that was recorded by the study physician when Dose 1 of HRV vaccine or placebo was administered. The subject received Dose 2 of HRV vaccine or placebo. Thereafter, the intensity of the gastrointestinal reflux changed from moderate to severe and the subject did not return for the study visit at the end of the first efficacy follow-up period. The AE was still ongoing at the last contact.

- One subject dropped out post Dose 2 of HRV vaccine or placebo after developing severe anaemia (grade 3 intensity) starting 254 days after Dose 2. The outcome of this event is not known.

- Subject dropped out post Dose 1 of HRV vaccine or placebo due to events following reaction to BCG vaccination (grade 3 intensity). The subject had received BCG vaccine 56 days before the first dose of HRV vaccine or placebo. The physician evaluating the subject prescribed antibiotics for a period of at least 6 months and asked for examination every 15 days. Due to these events the subject was withdrawn by the clinical study staff.

- One subject dropped out post Dose 2 of HRV vaccine or placebo after developing hypothyroidism (grade 1 intensity) starting on Day 108 after Dose 2. The AE was still ongoing at the last contact.

- One subject dropped out post Dose 1 of HRV vaccine or placebo after developing cervical lymphangioma (grade 2 intensity) starting on Day 117 after Dose 1. The AE was still ongoing at the last contact.

Two subjects dropped out with the reason stated as "protocol violation": one did not return for Visit 2 (received Dose 2 routine vaccines outside of the study) and one did not return for Visit 4 at the end of the first efficacy follow-up period.

Five subjects dropped out following advice from their family doctor. The reason for drop out was classified as "other" for these subjects.

4.2.3 Eligibility for analysis

Reasons for elimination from the ATP analyses are summarized in Table 12. See *Appendix A: Clintrial eligibility codes* for definitions of codes.

Table 12: Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses with reasons for exclusion

Title	Total	%	HRV $10^{4.7}$	HRV $10^{5.2}$	HRV $10^{5.8}$	Placebo
Number of vaccines prepared	**2759**		**689**	**690**	**690**	**690**
Subjects or vaccine number not allocated (code 1010)	604		151	150	150	153
Total enrolled cohort	**2155**		**538**	**540**	**540**	**537**
Total vaccinated cohort	**2155**	**100**	**538**	**540**	**540**	**537**
Administration of vaccine(s) forbidden in the protocol (code 1040)	38		10	11	8	9
Randomisation failure (code 1050)	4		0	1	2	1
Randomisation code broken at the investigator site (code 1060)	1		0	0	0	1
Study vaccine dose not administered according to protocol (code 1070)	96		20	27	19	30
Initially positive or unknown status for rotavirus on the day of Dose 1 (code 1500)	51		9	14	18	10
ATP cohort for safety analysis	**1965**	**91.2**	**499**	**487**	**493**	**486**
➢ Administration of any medication forbidden by the protocol (code 2040)	101		22	27	24	28
Concomitant infection by rotavirus other than vaccine strain which may influence immune response (code 2060)	45		7	8	5	25
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	88		18	21	26	23
Non compliance with blood sampling schedule (including wrong and unknown date) (code 2090)	58		19	9	15	15
Essential serological data missing (code 2100)	147		38	45	42	22
ATP cohort for immunogenicity analysis	**1526**	**70.8**	**395**	**377**	**381**	**373**
➢ At least one study vaccine dose not administered (code 3010)	80		21	26	22	11
Subjects not entered into the surveillance period of the first efficacy follow-up period (code 3020)	10		3	0	3	4
Concomitant infection by rotavirus other than vaccine strain up to 2 weeks after dose 2 which may influence efficacy response (code 3030)	29		7	1	4	17
ATP cohort for efficacy analysis for the first efficacy follow-up period	**1846**	**85.7**	**468**	**460**	**464**	**454**

Notes: % = percentage of subjects in the considered ATP cohort relative to the total vaccinated cohort
Comments: Subjects may have one or more elimination code(s) assigned for exclusion from a specific cohort. In that case the lowest code number is listed in the figure.
The ATP cohort for safety analysis includes all vaccinated subjects with no elimination codes beginning with one thousand. The ATP cohort for immunogenicity analysis includes all vaccinated subjects with no elimination codes beginning with one or two thousand. The ATP cohort for efficacy analysis during the first efficacy follow-up period includes all vaccinated subjects with no elimination codes beginning with one or three thousand.

ATP cohort for safety analysis

Of the 2155 subjects who were enrolled to receive two doses of HRV vaccine or placebo, 190 subjects were eliminated from ATP cohort for safety analysis for the following reasons:

- Thirty-eight subjects received vaccinations forbidden by the protocol (either OPV within 2 weeks of HRV vaccine or placebo dose or BCG/yellow fever vaccinations during the study).
- Randomization failed for four subjects: One subject received Dose 1 and Dose 2 of HRV vaccine or placebo assigned to him and one additional dose of study vaccine that was actually assigned to another subject. Three subjects received a wrong replacement vial.
- The randomization code was broken for one subject who had a SAE (death due to generalized visceral congestion). Refer to Section 6.2.6.2 for details of this case.
- Ninety-six subjects regurgitated within 30 minutes after oral administration of the HRV vaccine or placebo and may not have received the intended study vaccine dose.
- Fifty-one subjects were initially positive for RV or their RV status was unknown on the day of Dose 1 of HRV vaccine or placebo.

Thus, 1965 subjects were included in the ATP cohort for safety analysis.

ATP cohort for immunogenicity analysis

Of the 1965 subjects included in the ATP cohort for safety analysis, 439 subjects were eliminated from the ATP cohort for immunogenicity analysis for the following reasons:

- A total of 101 subjects were eliminated because they had received a medication forbidden by the protocol.
- GE stool samples collected between Visit 1 to Visit 3 from 45 subjects were positive for RV other than the vaccine strain.
- Eighty-eight subjects were eliminated due to non-compliance with vaccination schedule since they received Dose 2 of HRV vaccine or placebo outside of the interval of 49–83 days between vaccinations.
- Fifty-eight subjects were eliminated due to non-compliance with blood sampling schedule.

- A total of 147 subjects were eliminated because of essential immunogenicity (serum or stool analysis) data missing.

Thus, 1526 subjects were included in the ATP cohort for immunogenicity analysis.

ATP cohort for efficacy analysis
Of the 1965 subjects included in the ATP cohort for safety analysis, 119 subjects were eliminated from the ATP cohort for efficacy analysis for the first efficacy follow-up period for the following reasons:

- Eighty subjects did not receive the second dose of HRV vaccine or placebo.
- Ten subjects dropped out before the start of the first efficacy follow-up period.
- GE stool samples collected between Visit 1 to Visit 2 from 29 subjects were positive for RV other than the vaccine strain

Thus, 1846 subjects were included in the ATP cohort for efficacy analysis.

The number of subjects in the respective total vaccinated cohorts (efficacy, immunogenicity and safety) were determined based on the definition of cohorts in Section 3.15.4.

4.2.4 Compliance with protocol specified procedures

Written informed consent was obtained from parents/guardians of all subjects prior to entry in the study.

A total of 2004 of the 2155 enrolled subjects completed the study visit at the end of the first efficacy follow-up period. Therefore compliance with study completion until the end of the first efficacy follow-up period was 93%. Refer to Section 4.2.2 for further information.

Deviations from protocol-specified procedures that were considered as clinically relevant resulted in elimination of the subjects from analyses. Refer to Section 4.2.3 for further information.

The number of doses given and the number of completed symptom sheets (see definition in glossary of terms) for solicited symptoms, as well as the number of doses that were not given according to protocol for the total vaccinated cohort are detailed in Supplement 1. Symptom sheets were completed for the majority (> 97%) of doses in each group indicating high compliance for reactogenicity reporting. There were only few missing reactogenicity data indicating that symptom sheets were properly completed and this is an indication of good quality data. Subjects who regurgitated within 30 minutes and thus did not receive the dose according to the protocol were eliminated from ATP analyses (Refer to Section 4.2.3).

Subjects who did not respect the protocol-specified intervals between vaccinations or for blood sampling at Visit 2 and 3 were eliminated from the ATP cohort for immunogenicity analysis for subjects planned to receive two doses of HRV vaccine or placebo. Refer to Section 4.2.3. Supplement 2 presents deviations from specifications for age and intervals between visits stated in the study protocol.

For the ATP efficacy cohort, ELISA results for stool samples collected during GE episodes in the first efficacy follow-up period were not available for 23.1% episodes in the $10^{4.7}$ ffu HRV vaccine group, 28.3% episodes in the $10^{5.2}$ ffu HRV vaccine group, 29.8% episodes in the $10^{5.8}$ ffu HRV vaccine group and 22.7% episodes in the placebo group. Results were unavailable due to stool samples not collected during GE episodes or RV ELISA test not performed or an invalid result. See Supplement 3.

Weekly visits to the subjects' home by the Health Care workers were planned for GE surveillance. However, this activity was not to be documented and therefore compliance cannot be assessed.

Compliance for administration of routine DTPw-HB+Hib vaccine in the subset planned to receive two doses of HRV vaccine or placebo was as follows:

- In the total vaccinated cohort, more than 98% of subjects in each group received the DTPw-HB+Hib vaccine concomitantly with Dose 1 and Dose 2 of HRV vaccine or placebo.

- In the ATP cohort for immunogenicity, more than 98% of subjects in each group received the DTPw-HB+Hib vaccine concomitantly with Dose 1 and Dose 2 of HRV vaccine or placebo. None of the subjects received OPV concomitantly with Dose 1 and Dose 2 of HRV vaccine or placebo.

- In the ATP cohort for immunogenicity for subjects with available routine vaccination serology results at Visit 3, more than 93% of subjects in each group

received two doses of DTPw-HB+Hib and OPV vaccines between Visit 1 and before Visit 3.

- In the ATP cohort for immunogenicity for subjects with available routine vaccination serology results at the end of the first efficacy follow-up period, more than 94% of subjects in each group received three doses of DTPw-HB+Hib and OPV vaccines between Visit 1 and before the end of the first efficacy follow-up period.

4.3 Demographic characteristics

4.3.1 Total vaccinated cohort

Demographic characteristics for the total vaccinated cohort are summarized in Supplement 4. The mean age at the time of Dose 1 of HRV vaccine or placebo was 8.3 weeks (range 6–12 weeks). The mean age at the time of Dose 2 of HRV vaccine or placebo was 17.9 weeks (range 13–28 weeks). The demographic profile of the four groups was similar with respect to mean age, mean height and mean weight at the time of Dose 1 of HRV vaccine or placebo and race distribution. Observed differences in female to male ratio between the groups can be attributed to random chance and are not deemed clinically relevant.

Demographic characteristics by country are summarized in Supplement 5, Supplement 6 and Supplement 7. The demographic characteristics of the cohort differed between the countries for some aspects (e.g. mean age at Dose 1 of HRV vaccine or placebo and race distribution). However, for each given country, the demographic profile was similar between the four groups.

Supplement 8 presents the weight and height increases from Visit 1 to each of the subsequent visits until the end of the first efficacy follow-up period by group. The mean increase in height and weight from Visit 1 to Visits 2, 3 and 4 was similar among the four groups.

4.3.2 Subjects included in the ATP cohort for efficacy analysis

Demographic characteristics for the ATP cohort for efficacy analysis are summarized in Table 13. The demographic characteristics for the ATP cohort for efficacy analysis were similar to the demographic characteristics for the total vaccinated cohort.

Table 13: Summary of demographic characteristics (ATP cohort for efficacy analysis)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N = 468		HRV $10^{5.2}$ N = 460		HRV $10^{5.8}$ N = 464		Placebo N = 454		Total N = 1846	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age at first dose (weeks)	Mean	8.3	-	8.4	-	8.3	-	8.4	-	8.3	-
	SD	1.51	-	1.47	-	1.50	-	1.55	-	1.50	-
	Median	8	-	8	-	8	-	8	-	8	-
	Minimum	6	-	6	-	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	215	45.9	232	50.4	212	45.7	227	50.0	886	48.0
	Male	253	54.1	228	49.6	252	54.3	227	50.0	960	52.0
Race	Black	19	4.1	12	2.6	15	3.2	11	2.4	57	3.1
	White/Caucasian	98	20.9	116	25.2	124	26.7	111	24.4	449	24.3
	Oriental	0	0.0	0	0.0	0	0.0	1	0.2	1	0.1
	Other	351	75.0	332	72.2	325	70.0	331	72.9	1339	72.5
Height (cm)	Mean	57.4	-	57.5	-	57.5	-	57.6	-	57.5	-
	SD	2.75	-	2.59	-	2.90	-	2.92	-	2.80	-
	Median	57	-	58	-	57	-	58	-	57	-
	Unknown	2	-	1	-	1	-	1	-	5	-
Weight (kg)	Mean	5.3	-	5.3	-	5.3	-	5.3	-	5.3	-
	SD	0.75	-	0.67	-	0.74	-	0.76	-	0.70	-
	Median	5.2	-	5.3	-	5.3	-	5.3	-	5.3	-
	Unknown	2	-	0	-	1	-	1	-	4	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

4.3.3 Subjects included in the ATP cohort for immunogenicity analysis

Demographic characteristics for the subjects included in the ATP cohort for immunogenicity analysis are summarized in Supplement 9. The demographic characteristics for the ATP cohort for immunogenicity analysis were similar to the demographic characteristics for the total vaccinated cohort.

Supplement 10 presents the percentage of subjects who received OPV at birth. The proportion of subjects who received OPV at birth was similar for the four groups and ranged between 11.8% to 16.2%.

Supplement 11 presents a summary of feeding criteria on the day of each study vaccination by group. The feeding profile (percentage of subjects who were fed with breast milk, infant formula or both) of the four groups was similar. Most subjects were fed with breast milk or received both breast milk and infant formula. The percentage of subjects fed with breast milk decreased from Dose 1 to Dose 2 of HRV vaccine or placebo.

5 Analysis of efficacy in subjects planned to receive two doses of HRV vaccine or placebo

5.1 Data sets analyzed

Analysis of efficacy was performed on the ATP cohort (primary analysis) and the total vaccinated cohort. See Section 3.15.4 for definition of cohorts identified for analyses and Section 4.2.3 for description of eligibility for analyses.

5.2 ATP analysis

The ATP cohort for efficacy analysis consisted of 1846 subjects (468 subjects in the $10^{4.7}$ ffu HRV vaccine group, 460 subjects in the $10^{5.2}$ ffu HRV vaccine group, 464 subjects in the $10^{5.8}$ ffu HRV vaccine group and 454 subjects in the placebo group).

5.2.1 Characterization of GE episodes reported during the first efficacy follow-up period

The first efficacy follow-up period started from two weeks after Dose 2 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age).

The duration of follow-up was similar for the four groups, with a mean duration of 7 months. Refer to Supplement 12 for duration of follow-up for the first efficacy period.

Table 14 presents a summary of intensity of GE episodes of any etiology (RV or not) and RV GE episodes reported during the first efficacy follow-up period. Supplement 13 presents the percentage of subjects who reported GE episodes of any etiology (RV or not) and RV GE episodes during the first efficacy follow-up period.

During the first efficacy follow-up period, 411 GE episodes were reported for 197 subjects in the $10^{4.7}$ ffu HRV vaccine group, 385 GE episodes for 181 subjects in the $10^{5.2}$ ffu HRV vaccine group, 420 GE episodes for 195 subjects in the $10^{5.8}$ ffu HRV vaccine group and 419 GE episodes for 214 subjects in the placebo group (See Table 14 and Supplement 13). As seen from Supplement 13, the percentages of subjects who reported GE episodes of any etiology (RV or not) during the first efficacy follow-up period was similar between the groups: 42.1% in the $10^{4.7}$ ffu HRV vaccine group, 39.3% in the $10^{5.2}$ ffu HRV vaccine group, 42.0% in the $10^{5.8}$ ffu HRV vaccine group and 47.1% in the placebo group.

As seen from Table 14, a total of 109 RV GE episodes were reported during the first efficacy follow-up period. As seen from Supplement 13, the percentage of subjects reporting RV GE was lower in the three HRV vaccine groups (4.5% in the $10^{4.7}$ ffu HRV vaccine group, 4.8% in the $10^{5.2}$ ffu HRV vaccine group and 3.2% in the $10^{5.8}$ ffu HRV vaccine group) as compared to the placebo group (10.8%).

As seen from Supplement 13, no subject in the HRV vaccine groups had more than one episode of RV GE while two subjects from the placebo group had two episodes of RV GE (one subject had two episodes attributed to G1 wild-type RV while the other subject had one episode attributed to G9 type and one episode attributed to the G1 wild-type RV).

As seen from Table 14, 57.1% of RV GE episodes in the $10^{4.7}$ ffu HRV vaccine group, 45.5% of RV GE episodes in the $10^{5.2}$ ffu HRV vaccine group, 33.3% of RV GE episodes in the $10^{5.8}$ ffu HRV vaccine group and 66.7% of RV GE episodes in the placebo group were noted as severe (a score ≥ 11 on a 20-point scale).

Table 14: Number of GE episodes and RV GE episodes reported during the first efficacy follow-up period, by severity (ATP cohort for efficacy analysis)

		HRV $10^{4.7}$		**HRV $10^{5.2}$**		**HRV $10^{5.8}$**		**Placebo**	
Event	**Severity**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
GE of any etiology (RV or not)	**Mild (1-6)**	190	46.2	202	52.5	214	51.0	185	44.2
	Moderate (7-10)	127	30.9	114	29.6	132	31.4	123	29.4
	Severe (≥11)	94	22.9	69	17.9	74	17.6	111	26.5
	Any	411	100	385	100	420	100	419	100
RV GE	**Mild (1-6)**	4	19.0	8	36.4	2	13.3	5	9.8
	Moderate (7-10)	5	23.8	4	18.2	8	53.3	12	23.5
	Severe (≥11)	12	57.1	10	45.5	5	33.3	34	66.7
	Any	21	100	22	100	15	100	51	100

Notes: n/% = number/percentage of GE or RV GE episodes reported in each group, by severity, among all GE or RV GE episodes reported in the first efficacy follow-up period
Any = any specified symptom, regardless of severity

Stool analysis results were not available for 26% of the reported GE cases due to stool samples not collected during GE episodes or RV ELISA test not performed or invalid result. Refer to Section 4.2.4.

Table 15 presents the percentage of subjects reporting RV GE episodes during the first efficacy follow-up period by RV G type.

The predominant RV types during the first efficacy follow-up period were wild-type G1 (identified in 50.5% of RV GE episodes) and G9 (identified in 39.4% of RV GE episodes). In addition, G2, G3 and G4 types were also isolated during the first efficacy follow-up period. RV G type could not be identified for two subjects in the $10^{5.2}$ ffu HRV vaccine group.

Table 15: Percentage of subjects with RV GE episodes reported during the first efficacy follow-up period, by RV G type (ATP cohort for efficacy analysis)

Type	HRV $10^{4.7}$ N = 468		HRV $10^{5.2}$ N = 460		HRV $10^{5.8}$ N = 464		Placebo N = 454	
	n	%	n	%	n	%	n	%
Any	21	4.5	22	4.8	15	3.2	49	10.8
G1 wild type	12	2.6	6	1.3	7	1.5	29	6.4
G2	0	0.0	0	0.0	1	0.2	3	0.7
G3	1	0.2	0	0.0	0	0.0	2	0.4
G4	0	0.0	0	0.0	1	0.2	0	0.0
G9	8	1.7	14	3.0	7	1.5	15	3.3
Canine	0	0.0	0	0.0	0	0.0	1	0.2
Unknown	0	0.0	2	0.4	0	0.0	0	0.0

Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified type in each group
Any = RV GE episode, whatever the type

Supplement 14 presents the characteristics of GE episodes reported during the first efficacy follow-up period. The rate of hospitalization was lower in the HRV vaccine groups as compared to the placebo group while other characteristics of GE episodes were similar between the groups.

Supplement 15 presents the characteristics of RV GE episodes reported during the first efficacy follow-up period. As seen from Supplement 15, the duration of vomiting and diarrhea, level of dehydration and rate of hospitalization for any RV GE episodes were lower in the HRV vaccine groups as compared to the placebo group. Supplement 16 and Supplement 17 respectively present the characteristics of RV GE episodes caused by G1 wild-type and G9 type reported during the first efficacy follow-up period.

Supplement 18 presents the percentage of RV GE episodes with mixed infections during the first efficacy follow-up period. No concurrent pathogen was identified in the majority (94.5%) of RV GE episodes. Only six mixed RV GE episodes were reported (one in the $10^{4.7}$ ffu HRV vaccine group, two in the $10^{5.8}$ ffu HRV vaccine group and three in the placebo group).

Supplement 19 presents the percentage of subjects in the HRV vaccine groups reporting RV GE according to the serological status of anti-rotavirus IgA antibodies at two months after Dose 2 of HRV vaccine or placebo.

5.2.2 Vaccine efficacy against RV GE during the first efficacy follow-up period

Table 16 presents the efficacy of the HRV vaccine against RV GE of any intensity during the first efficacy follow-up period. Table 17 presents the efficacy of the vaccine against severe RV GE during the first efficacy follow-up period.

There was a statistically significant decrease in the percentage of subjects reporting any RV GE and severe RV GE during the first efficacy follow-up period in pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group (p-value < 0.001, two-sided Fisher's exact test). The primary objective (efficacy against any RV GE from 2 weeks after Dose 2 of HRV vaccine or placebo until the end of the efficacy follow-up period) of the study was reached.

There was a trend towards increased efficacy against any and severe RV GE in the $10^{5.8}$ ffu HRV vaccine group *versus* other HRV vaccine groups.

Table 16: Percentage of subjects reporting any RV GE and efficacy of the vaccine during the first efficacy follow-up period (ATP cohort for efficacy analysis)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**p-value**
HRV $10^{4.7}$	468	21	276.4	0.076	0.050	0.117	4.5	2.8	6.8	58.4	29.4	76.3	<0.001
HRV $10^{5.2}$	460	22	268.4	0.082	0.054	0.124	4.8	3.0	7.2	55.7	25.3	74.5	<0.001
HRV $10^{5.8}$	464	15	272.2	0.055	0.033	0.091	3.2	1.8	5.3	70.0	45.7	84.4	<0.001
Pooled HRV Groups	1392	58	817.0	0.071	0.055	0.092	4.2	3.2	5.4	61.4	42.3	74.1	<0.001
Placebo	454	49	256.5	0.191	0.144	0.253	10.8	8.1	14.0	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one RV GE episode in each group
n/T = person-year rate of RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Table 17: Percentage of subjects reporting severe RV GE and efficacy of the vaccine during the first efficacy follow-up period (ATP cohort for efficacy analysis)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**p-value**
HRV $10^{4.7}$	468	12	279.7	0.043	0.024	0.076	2.6	1.3	4.4	65.8	32.2	83.9	<0.001
HRV $10^{5.2}$	460	10	273.1	0.037	0.020	0.068	2.2	1.0	4.0	71.0	39.9	87.2	<0.001
HRV $10^{5.8}$	464	5	276.1	0.018	0.008	0.044	1.1	0.4	2.5	85.6	63.0	95.6	<0.001
Pooled HRV Groups	1392	27	828.9	0.033	0.022	0.047	1.9	1.3	2.8	74.1	55.8	85.0	<0.001
Placebo	454	34	261.7	0.130	0.093	0.182	7.5	5.2	10.3	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Vaccine efficacy rates against the primary endpoint (occurrence of any RV GE from 2 weeks after Dose 2 of HRV vaccine or placebo until the end of the efficacy follow-up period) estimated by the Cox proportional-hazard model were similar to vaccine efficacy estimates presented in this section.

Supplement 20 presents vaccine efficacy against any RV GE during the first efficacy follow-up period by G type.

- There was a statistically significant decrease in the percentage of subjects reporting any RV GE caused by G1 wild-type during the first efficacy follow-up period in pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test).

- There was a statistically significant decrease in the percentage of subjects reporting any RV GE caused by non-G1 types (either G2, G3, G4 or G9 type) during the first efficacy follow-up period in pooled HRV vaccine groups, in $10^{4.7}$ ffu HRV vaccine group and in $10^{5.8}$ ffu HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test). The percentage of subjects reporting any RV GE caused by non-G1 types was lower, although not statistically significant, in the $10^{5.2}$ ffu HRV vaccine group as compared to the placebo group.

- The percentage of subjects reporting any RV GE caused by G9 type during the first efficacy follow-up period was lower in pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group, but the difference did not reach statistical significance (p-value > 0.05, two-sided Fisher's exact test).

Supplement 21 presents the efficacy of the vaccine against severe RV GE during the first efficacy follow-up period by G type.

- There was a statistically significant decrease in the percentage of subjects reporting severe RV GE caused by G1 wild-type during the first efficacy follow-up period in pooled HRV vaccine groups, in $10^{5.2}$ ffu HRV vaccine group, $10^{5.8}$ ffu HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test). The percentage of subjects reporting severe RV GE caused by G1 wild-type was lower in the $10^{4.7}$ ffu HRV vaccine group as compared to the placebo group, but the difference did not reach statistical significance (p-value > 0.05, two-sided Fisher's exact test).

- There was a statistically significant decrease in the percentage of subjects reporting severe RV GE caused by non-G1 types (either G2, G3, G4 or G9 type) during the first efficacy follow-up period in pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test).

- There was a statistically significant decrease in the percentage of subjects reporting severe RV GE caused by G9 type during the first efficacy follow-up period in pooled HRV vaccine groups, in $10^{4.7}$ ffu HRV vaccine group and in $10^{5.8}$ ffu HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test). The percentage of subjects reporting severe RV GE caused by G9 type was lower, although not statistically significant, in the $10^{5.2}$ ffu HRV vaccine group as compared to the placebo group.

Supplement 22 and Supplement 23 respectively present vaccine efficacy against any and severe RV GE during the first efficacy follow-up period by country.

The vaccine efficacy against any and severe RV GE was lower in Brazil when compared to Mexico and Venezuela. There was a statistically significant decrease in the percentage of subjects reporting any and severe RV GE in pooled HRV vaccine groups in each country as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test).

In each country, there was a statistically significant decrease in the percentage of subjects reporting any RV GE in all HRV vaccine groups as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test), except for $10^{4.7}$ and $10^{5.2}$ ffu HRV vaccine groups in Brazil.

In each country, there was a statistically significant decrease in the percentage of subjects reporting severe RV GE in each HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test), except for $10^{4.7}$ ffu HRV vaccine group in Mexico and Venezuela.

Since no concurrent pathogen was identified in the majority (94.5%) of RV GE episodes, vaccine efficacy against pure and mixed RV GE during the first efficacy follow-up period was not evaluated.

5.2.3 Vaccine efficacy against hospitalization due to RV GE during the first efficacy follow-up period

Table 18 presents the efficacy against hospitalization due to RV GE during the first efficacy follow-up period.

There was a statistically significant decrease in the percentage of subjects hospitalized due to RV GE during the first efficacy follow-up period in pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test).

Table 18: Percentage of subjects hospitalized due to RV GE and efficacy of the vaccine during the first efficacy follow-up period (ATP cohort for efficacy analysis)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**p-value**
HRV $10^{4.7}$	468	5	281.4	0.018	0.007	0.043	1.1	0.3	2.5	65.4	-1.8	90.2	0.037
HRV $10^{5.2}$	460	1	276.1	0.004	0.001	0.026	0.2	0.0	1.2	93.0	53.7	99.8	<0.001
HRV $10^{5.8}$	464	3	276.8	0.011	0.003	0.034	0.6	0.1	1.9	79.0	24.9	96.1	0.007
Pooled HRV Groups	1392	9	834.3	0.011	0.006	0.021	0.6	0.3	1.2	79.0	48.0	92.0	<0.001
Placebo	454	14	267.7	0.052	0.031	0.088	3.1	1.7	5.1	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects hospitalized due to RV GE in each group
T= sum of follow-up period expressed in year censored at the first occurrence of hospitalization due to RV GE episode in the first efficacy follow-up period, in each group
n/N= percentage of subjects hospitalized due to RV GE in each group
n/T= person-year rate of hospitalization due to RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

5.2.4 Total vaccinated cohort for efficacy analysis

The total vaccinated cohort for analysis of efficacy during the first efficacy follow-up period consisted of 2044 subjects (507 subjects in the $10^{4.7}$ ffu HRV vaccine group, 508 subjects in the $10^{5.2}$ ffu HRV vaccine group, 512 subjects in the $10^{5.8}$ ffu HRV vaccine group and 517 subjects the placebo group).

Efficacy data during the first efficacy follow-up period for the total vaccinated cohort are presented in Supplement 24 to Supplement 39.

The results of the total vaccinated cohort analyses were consistent with those observed in the ATP cohort.

5.2.4.1 Vaccine efficacy against RV GE occurring from Dose 1 onwards

In order to have a first look at the effectiviness of the vaccine from the first dose onwards, occurrence of RV GE episodes from Day of Dose1 till Day 14 of Dose 2 and occurrence of RV GE episodes from Day of Dose1 till the end of the first efficacy follow-up period were evaluated.

The total vaccinated cohort for analysis of RV GE occurring from day of Dose 1 onwards consisted of 2155 subjects (538 subjects in the $10^{4.7}$ ffu HRV vaccine group, 540 subjects in the $10^{5.2}$ ffu HRV vaccine group, 540 subjects in the $10^{5.8}$ ffu HRV vaccine group and 537 subjects the placebo group).

Occurrence of RV GE from day of Dose 1 till Day 14 after Dose 2 of HRV vaccine or placebo

Supplement 40 presents the percentage of subjects in each group who reported any or severe RV GE episode(s) from day of Dose 1 till Day 14 after Dose 2. Supplement 40 includes all RV GE episodes caused by wild-type and vaccine strain RV. The percentages of subjects reporting RV GE tended to be lower in the pooled HRV groups and in each HRV vaccine group (2.0–2.6%) as compared to the placebo group (3.7%). The percentages of subjects reporting severe RV GE tended to be lower in the pooled HRV groups and in each HRV vaccine group (0.4–0.9%) as compared to the placebo group (1.9%).

Stool analysis results were not available for 25% of the reported GE cases due to stool samples not collected during GE episodes or RV ELISA test not performed or invalid result.

Among RV GE episodes reported from day of Dose 1 till Day 14 after Dose 2, G1 vaccine strain RV was detected in 28.6–46.2% RV GE episodes in the HRV vaccine groups. In addition, G1 wild-type, G2 and G9 types were also isolated in the HRV vaccine groups. RV G type could not be identified/was not tested for two subjects in the $10^{4.7}$ ffu HRV vaccine group, three subjects in the $10^{5.2}$ ffu HRV vaccine group and two subjects in the $10^{5.8}$ ffu HRV vaccine group. The serotypes identified in the placebo group were wild-type G1 (50% of RV GE episodes), G9 (40% of RV GE episodes) and G2 (10% of RV GE episodes). From day of Dose 1 till Day 14 after Dose 2, severe RV GE episodes attributed to the G1 vaccine strain were reported infrequently (two subjects in the $10^{5.2}$ ffu HRV vaccine group and one subject in the $10^{5.8}$ ffu HRV vaccine group).

Supplement 41 presents vaccine efficacy against any and severe RV GE during the period starting from day of Dose 1 till Day 14 of Dose 2. Supplement 41 did not include RV GE episodes caused by the vaccine strain RV. The percentages of subjects reporting RV GE (any and severe intensity), caused by RV other than the vaccine strain, tended to be lower in the pooled HRV groups and in each HRV vaccine group as compared to the placebo group. Vaccine efficacy for the pooled HRV vaccine groups was 63.5% [95% CI, 29.5– 81.0] against any RV GE and 73.4% [95% CI, 25.3–90.9] against severe RV GE. These results were similar with those observed for the efficacy from day of Dose 1 till the end of the first efficacy follow-up period and from 2 weeks post Dose 2 till the end of the first efficacy follow-up period.

Occurrence of RV GE from day of Dose 1 till the end of the first efficacy follow-up period

Of the 2155 subjects enrolled in the study, 99 subjects received only one dose of HRV vaccine or placebo and the remaining received two doses of HRV vaccine or placebo (see Table 19). The vaccine efficacy from day of Dose 1 till the end of the first efficacy follow-up period is the efficacy for subjects receiving at least one dose of HRV vaccine or placebo but taking into account also the RV GE episodes that occurred from the day of Dose 1 till Day 14 of Dose 2. This analysis thus considers the effect of the first dose by looking at the number of RV GE episodes occuring between Dose 1 and Dose 2 in vaccine groups *versus* placebo.

Stool analysis results were not available for 26% of the reported GE cases due to stool samples not collected during GE episodes or RV ELISA test not performed or invalid result.

Analysis of RV GE occurring from day of Dose 1 till the end of the first efficacy follow-up period excluded all RV GE episodes caused by the vaccine strain RV.

Supplement 42 presents vaccine efficacy against any and severe RV GE during the period starting from day of Dose 1 till the end of the first efficacy follow-up period.

There was a statistically significant decrease in the percentage of subjects reporting RV GE (any and severe intensity) in pooled HRV groups and in each HRV group as compared to the placebo group (p-value < 0.05, two-sided Fisher's exact test). Vaccine efficacy for the pooled HRV vaccine groups was 64.2% [95% CI, 50.3–74.1] against any RV GE and 76.1% [95% CI, 62.6–84.9] against severe RV GE. These results were similar with those observed for the efficacy from 2 weeks post Dose 2 till the end of the first efficacy follow-up period.

6 Analysis of safety in subjects planned to receive two doses of HRV vaccine or placebo

6.1 Data sets analyzed

Analysis of safety was performed on the total vaccinated cohort (primary analysis) and the ATP cohort for safety analysis since more than 5% of subjects were eliminated from the ATP cohort for safety analysis. See Section 3.15.4 for description of analyses cohorts and Section 4.2.3 for explanation of eligibility for analysis.

6.2 Total vaccinated cohort for safety analysis

The total vaccinated cohort for analysis of safety consisted of 2155 subjects (538 subjects in the $10^{4.7}$ ffu HRV vaccine group, 540 subjects in the $10^{5.2}$ ffu HRV vaccine group, 540 subjects in the $10^{5.8}$ ffu HRV vaccine group and 537 subjects the placebo group).

Table 19 presents the exposure to vaccination by group and overall.

Table 19: Number and percentage of subjects who received vaccine dose(s) (total vaccinated cohort for safety analysis)

Total number of doses received	HRV $10^{4.7}$ (N = 538)		HRV $10^{5.2}$ (N = 540)		HRV $10^{5.8}$ (N = 540)		Placebo (N = 537)		Total (N = 2155)	
	n	%	n	%	n	%	n	%	n	%
0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
1	28	5.2	31	5.7	25	4.6	15	2.8	99	4.6
2	510	94.8	509	94.3	515	95.4	522	97.2	2056	95.4
Any	538	100	540	100	540	100	537	100	2155	100

Notes: N = number of subjects in each group or in total (sum of all groups)
n/% = number/percentage of subjects receiving the specified total number of doses of HRV vaccine or placebo in each group or in total
Any = number and percentage of subjects receiving at least one dose of HRV vaccine or placebo

Of the 99 subjects who received only one dose of HRV vaccine or placebo, one subject was a drop out due to SAE (death unrelated to vaccination), one subject was a drop out due to vaccination-related non-serious AE, two subjects were drop outs due to vaccination-unrelated non-serious AE and 45 subjects were drop outs due to consent withdrawal. Refer to Section 4.2.2 and Section 6.2.6.2 for further details on these subjects.

6.2.1 Overall incidence of symptoms

Table 20 presents the percentages of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15-day solicited follow-up period.

The majority of subjects in each group reported symptoms (solicited or unsolicited) during the 15-day solicited follow-up period. It should be noted that the majority (more than 98%) of subjects received routine DTPw-HB+Hib vaccine concomitantly with HRV vaccine or placebo and DTPw-based vaccines are known to be highly reactogenic. The incidence rates were similar between groups with very narrow and overlapping 95% CIs. Incidences of symptoms rated as grade "3" in intensity and those assessed as related to vaccination were also similar between the groups. There was no increase in incidence of symptoms (solicited or unsolicited) with subsequent doses of HRV vaccine or with increased viral concentration.

Table 20: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15-day solicited follow-up period (total vaccinated cohort for safety analysis)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	HRV $10^{4.7}$	538	490	91.1	88.3	93.3
	HRV $10^{5.2}$	540	491	90.9	88.2	93.2
	HRV $10^{5.8}$	540	495	91.7	89.0	93.9
	Pooled HRV groups	1618	1476	91.2	89.7	92.6
	Placebo	537	500	93.1	90.6	95.1
Dose 2	HRV $10^{4.7}$	510	437	85.7	82.3	88.6
	HRV $10^{5.2}$	509	449	88.2	85.1	90.9
	HRV $10^{5.8}$	515	451	87.6	84.4	90.3
	Pooled HRV groups	1534	1337	87.2	85.4	88.8
	Placebo	522	457	87.5	84.4	90.3
Overall/dose	HRV $10^{4.7}$	1048	927	88.5	86.4	90.3
	HRV $10^{5.2}$	1049	940	89.6	87.6	91.4
	HRV $10^{5.8}$	1055	946	89.7	87.7	91.4
	Pooled HRV groups	3152	2813	89.2	88.1	90.3
	Placebo	1059	957	90.4	88.4	92.1
Overall/subject	HRV $10^{4.7}$	538	514	95.5	93.4	97.1
	HRV $10^{5.2}$	540	516	95.6	93.5	97.1
	HRV $10^{5.8}$	540	515	95.4	93.2	97.0
	Pooled HRV groups	1618	1545	95.5	94.4	96.4
	Placebo	537	521	97.0	95.2	98.3

Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For each dose:
N = number of subjects having received the considered dose of HRV vaccine or placebo
n/% = number/percentage of subjects reporting at least one symptom for the considered dose of HRV vaccine or placebo
For overall/dose:
N = total number of doses of HRV vaccine or placebo administered
n/% = total number/percentage of doses of HRV vaccine or placebo reporting at least one symptom
For overall/subject:
N= number of subjects having received at least one dose of HRV vaccine or placebo
n/%= number percentage of subjects reporting at least one symptom

Supplement 43 and Supplement 44 respectively present the percentage of doses and of subjects reporting grade "3" and related symptoms (solicited or unsolicited) during the 15-day solicited follow-up period.

6.2.2 Solicited signs and symptoms

Table 21 and Table 22 present the percentage of subjects with specific solicited symptoms including those graded "2 or 3" in intensity, those graded "3" in intensity and those considered to be related to vaccination, during the 15-day solicited follow-up period after each dose of HRV vaccine or placebo.

Supplement 45 presents the percentage of doses and subjects reporting specific solicited symptoms including those graded "2 or 3" in intensity, those graded "3" in intensity and those considered to be related to vaccination, during the 15-day solicited follow-up period after any doses of HRV vaccine or placebo.

Cough/runny nose, fever and irritability were the most commonly reported solicited symptoms in all groups. Diarrhea was the least frequently reported solicited general symptom. Incidences were similar between the groups for each solicited symptom including those rated as grade "2 or 3" in intensity, rated as grade "3" in intensity and those assessed as related to vaccination. There was no apparent increase in incidence of solicited symptoms after Dose 2 as compared to Dose 1 of HRV vaccine or placebo.

Table 21: Percentage of subjects with each solicited symptom including those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period ***after Dose 1*** *of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Solicited symptom		**HRV $10^{4.7}$ N = 538**				**HRV $10^{5.2}$ N = 540**				**HRV $10^{5.8}$ N = 540**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**			**LL**	**UL**
Cough/ runny nose	Total	325	60.4	56.1	64.6	316	58.5	54.2	62.7	322	59.6	55.4	63.8
	Grade 2 or 3	171	31.8	27.9	35.9	150	27.8	24.0	31.8	167	30.9	27.0	35.0
	Grade 3	45	8.4	6.2	11.0	51	9.4	7.1	12.2	53	9.8	7.4	12.6
	Related	109	20.3	16.9	23.9	102	18.9	15.7	22.4	91	16.9	13.8	20.3
Diarrhea	Total	33	6.1	4.3	8.5	34	6.3	4.4	8.7	44	8.1	6.0	10.8
	Grade 2 or 3	19	3.5	2.1	5.5	24	4.4	2.9	6.5	28	5.2	3.5	7.4
	Grade 3	8	1.5	0.6	2.9	11	2.0	1.0	3.6	11	2.0	1.0	3.6
	Related	16	3.0	1.7	4.8	20	3.7	2.3	5.7	29	5.4	3.6	7.6
Irritability/ fussiness	Total	381	70.8	66.8	74.6	380	70.4	66.3	74.2	391	72.4	68.4	76.1
	Grade 2 or 3	251	46.7	42.4	51.0	241	44.6	40.4	48.9	259	48.0	43.7	52.3
	Grade 3	65	12.1	9.4	15.1	69	12.8	10.1	15.9	75	13.9	11.1	17.1
	Related	236	43.9	39.6	48.2	227	42.0	37.8	46.3	241	44.6	40.4	48.9
Loss of appetite	Total	170	31.6	27.7	35.7	176	32.6	28.7	36.7	171	31.7	27.8	35.8
	Grade 2 or 3	50	9.3	7.0	12.1	50	9.3	7.0	12.0	70	13.0	10.2	16.1
	Grade 3	6	1.1	0.4	2.4	7	1.3	0.5	2.7	11	2.0	1.0	3.6
	Related	74	13.8	11.0	17.0	78	14.4	11.6	17.7	78	14.4	11.6	17.7
Fever	Total	331	61.5	57.3	65.7	339	62.8	58.5	66.9	332	61.5	57.2	65.6
	Grade 2 or 3	127	23.6	20.1	27.4	110	20.4	17.1	24.0	126	23.3	19.8	27.1
	Grade 3	6	1.1	0.4	2.4	7	1.3	0.5	2.7	8	1.5	0.6	2.9
	Related	205	38.1	34.0	42.4	189	35.0	31.0	39.2	189	35.0	31.0	39.2
Vomiting	Total	88	16.4	13.3	19.8	106	19.6	16.4	23.2	91	16.9	13.8	20.3
	Grade 2 or 3	35	6.5	4.6	8.9	61	11.3	8.8	14.3	43	8.0	5.8	10.6
	Grade 3	12	2.2	1.2	3.9	25	4.6	3.0	6.8	22	4.1	2.6	6.1
	Related	48	8.9	6.7	11.7	46	8.5	6.3	11.2	40	7.4	5.3	10.0

Notes: N = number of subjects having received Dose 1 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 1 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 21 (continued): Percentage of subjects with each solicited symptom including those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period ***after Dose 1*** *of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Solicited symptom		**Pooled HRV groups N = 1618**				**Placebo N = 537**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
Cough/ runny nose	Total	963	59.5	57.1	61.9	340	63.3	59.1	67.4
	Grade 2 or 3	488	30.2	27.9	32.5	182	33.9	29.9	38.1
	Grade 3	149	9.2	7.8	10.7	34	6.3	4.4	8.7
	Related	302	18.7	16.8	20.7	105	19.6	16.3	23.2
Diarrhea	Total	111	6.9	5.7	8.2	45	8.4	6.2	11.1
	Grade 2 or 3	71	4.4	3.4	5.5	27	5.0	3.3	7.2
	Grade 3	30	1.9	1.3	2.6	10	1.9	0.9	3.4
	Related	65	4.0	3.1	5.1	23	4.3	2.7	6.4
Irritability/ fussiness	Total	1152	71.2	68.9	73.4	408	76.0	72.1	79.5
	Grade 2 or 3	751	46.4	44.0	48.9	272	50.7	46.3	55.0
	Grade 3	209	12.9	11.3	14.6	82	15.3	12.3	18.6
	Related	704	43.5	41.1	46.0	243	45.3	41.0	49.6
Loss of appetite	Total	517	32.0	29.7	34.3	187	34.8	30.8	39.0
	Grade 2 or 3	170	10.5	9.1	12.1	65	12.1	9.5	15.2
	Grade 3	24	1.5	1.0	2.2	8	1.5	0.6	2.9
	Related	230	14.2	12.5	16.0	87	16.2	13.2	19.6
Fever	Total	1002	61.9	59.5	64.3	346	64.4	60.2	68.5
	Grade 2 or 3	363	22.4	20.4	24.5	126	23.5	19.9	27.3
	Grade 3	21	1.3	0.8	2.0	11	2.0	1.0	3.6
	Related	583	36.0	33.7	38.4	192	35.8	31.7	40.0
Vomiting	Total	285	17.6	15.8	19.6	89	16.6	13.5	20.0
	Grade 2 or 3	139	8.6	7.3	10.1	43	8.0	5.9	10.6
	Grade 3	59	3.6	2.8	4.7	13	2.4	1.3	4.1
	Related	134	8.3	7.0	9.7	54	10.1	7.6	12.9

Notes: N = number of subjects having received Dose 1 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 1 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 22: Percentage of subjects with each solicited symptom including those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period ***after Dose 2*** *of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Solicited symptom		**HRV $10^{4.7}$ N = 510**				**HRV $10^{5.2}$ N = 509**				**HRV $10^{5.8}$ N = 515**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**			**LL**	**UL**
Cough/ runny nose	Total	310	60.8	56.4	65.0	323	63.5	59.1	67.7	334	64.9	60.6	69.0
	Grade 2 or 3	164	32.2	28.1	36.4	163	32.0	28.0	36.3	176	34.2	30.1	38.5
	Grade 3	51	10.0	7.5	12.9	51	10.0	7.6	13.0	56	10.9	8.3	13.9
	Related	97	19.0	15.7	22.7	110	21.6	18.1	25.4	109	21.2	17.7	25.0
Diarrhea	Total	38	7.5	5.3	10.1	34	6.7	4.7	9.2	44	8.5	6.3	11.3
	Grade 2 or 3	29	5.7	3.8	8.1	23	4.5	2.9	6.7	29	5.6	3.8	8.0
	Grade 3	8	1.6	0.7	3.1	12	2.4	1.2	4.1	13	2.5	1.4	4.3
	Related	19	3.7	2.3	5.8	23	4.5	2.9	6.7	21	4.1	2.5	6.2
Irritability/ fussiness	Total	292	57.3	52.8	61.6	303	59.5	55.1	63.8	313	60.8	56.4	65.0
	Grade 2 or 3	163	32.0	27.9	36.2	166	32.6	28.6	36.9	191	37.1	32.9	41.4
	Grade 3	53	10.4	7.9	13.4	43	8.4	6.2	11.2	49	9.5	7.1	12.4
	Related	168	32.9	28.9	37.2	173	34.0	29.9	38.3	177	34.4	30.3	38.6
Loss of appetite	Total	149	29.2	25.3	33.4	146	28.7	24.8	32.8	152	29.5	25.6	33.7
	Grade 2 or 3	67	13.1	10.3	16.4	62	12.2	9.5	15.3	61	11.8	9.2	15.0
	Grade 3	14	2.7	1.5	4.6	16	3.1	1.8	5.1	4	0.8	0.2	2.0
	Related	59	11.6	8.9	14.7	54	10.6	8.1	13.6	53	10.3	7.8	13.2
Fever	Total	275	53.9	49.5	58.3	272	53.4	49.0	57.8	279	54.2	49.8	58.5
	Grade 2 or 3	106	20.8	17.3	24.6	116	22.8	19.2	26.7	114	22.1	18.6	26.0
	Grade 3	9	1.8	0.8	3.3	13	2.6	1.4	4.3	14	2.7	1.5	4.5
	Related	139	27.3	23.4	31.3	127	25.0	21.2	28.9	143	27.8	23.9	31.9
Vomiting	Total	55	10.8	8.2	13.8	69	13.6	10.7	16.8	65	12.6	9.9	15.8
	Grade 2 or 3	27	5.3	3.5	7.6	41	8.1	5.8	10.8	37	7.2	5.1	9.8
	Grade 3	13	2.5	1.4	4.3	21	4.1	2.6	6.2	20	3.9	2.4	5.9
	Related	32	6.3	4.3	8.7	33	6.5	4.5	9.0	23	4.5	2.9	6.6

Notes: N = number of subjects having received Dose 2 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 2 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 22(continued): Percentage of subjects with each solicited symptom including those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period ***after Dose 2*** *of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Solicited symptom		**Pooled HRV groups N = 1534**				**Placebo N = 522**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
Cough/ runny nose	Total	967	63.0	60.6	65.5	331	63.4	59.1	67.6
	Grade 2 or 3	503	32.8	30.4	35.2	190	36.4	32.3	40.7
	Grade 3	158	10.3	8.8	11.9	46	8.8	6.5	11.6
	Related	316	20.6	18.6	22.7	103	19.7	16.4	23.4
Diarrhea	Total	116	7.6	6.3	9.0	46	8.8	6.5	11.6
	Grade 2 or 3	81	5.3	4.2	6.5	33	6.3	4.4	8.8
	Grade 3	33	2.2	1.5	3.0	15	2.9	1.6	4.7
	Related	63	4.1	3.2	5.2	20	3.8	2.4	5.9
Irritability/ fussiness	Total	908	59.2	56.7	61.7	305	58.4	54.1	62.7
	Grade 2 or 3	520	33.9	31.5	36.3	177	33.9	29.9	38.1
	Grade 3	145	9.5	8.0	11.0	42	8.0	5.9	10.7
	Related	518	33.8	31.4	36.2	164	31.4	27.5	35.6
Loss of appetite	Total	447	29.1	26.9	31.5	149	28.5	24.7	32.6
	Grade 2 or 3	190	12.4	10.8	14.1	69	13.2	10.4	16.4
	Grade 3	34	2.2	1.5	3.1	12	2.3	1.2	4.0
	Related	166	10.8	9.3	12.5	58	11.1	8.5	14.1
Fever	Total	826	53.8	51.3	56.4	288	55.2	50.8	59.5
	Grade 2 or 3	336	21.9	19.9	24.1	96	18.4	15.2	22.0
	Grade 3	36	2.3	1.6	3.2	11	2.1	1.1	3.7
	Related	409	26.7	24.5	29.0	125	23.9	20.3	27.8
Vomiting	Total	189	12.3	10.7	14.1	59	11.3	8.7	14.3
	Grade 2 or 3	105	6.8	5.6	8.2	30	5.7	3.9	8.1
	Grade 3	54	3.5	2.7	4.6	15	2.9	1.6	4.7
	Related	88	5.7	4.6	7.0	24	4.6	3.0	6.8

Notes: N = number of subjects having received Dose 2 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 2 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Incidence of each individual solicited symptom during the first 3 days (Day 0 to Day 2) and during the first 8 days (Day 0 to Day 7) after vaccination were calculated since replication of the vaccine virus peaks during the first 8 days after vaccination ([1]). Incidences by onset of symptoms were similar between the groups, with the majority of symptoms occurring within 8 days after vaccination. Only inferential analyses on percentage of subjects reporting each individual solicited symptom within the 8-day (Days 0 to Day 7) after vaccination are presented in this study report.

Table 23 presents statistical comparisons between groups for percentage of subjects reporting each solicited symptom after any dose of HRV vaccine or placebo.

Statistically significant differences were detected between the HRV $10^{4.7}$ group (8.4%) *versus* the HRV $10^{5.2}$ group (12.4%) with respect to the percentage of subjects reporting grade "2 or 3" vomiting after any dose of HRV vaccine or placebo during an 8-day follow-up period (p-value = 0.036, two-sided Fisher's exact test). No other statistically significant differences were detected for the comparison between the pooled HRV vaccine groups or the three HRV vaccine groups *versus* the placebo group with respect to the incidence of subjects reporting individual solicited symptoms (fever, fussiness/irritability, diarrhea, vomiting, loss of appetite and cough/runny nose) (p-value > 0.05, two-sided Fisher's exact test). Importantly, statistically significant differences were not detected for the clinically important grade "3" symptoms. Any statistically significant differences should be interpreted cautiously since, due to the number of endpoints the differences observed in this study are likely to occur by chance alone.

Table 23: Statistical comparisons between groups for percentage of subjects reporting each solicited symptom after any dose of HRV vaccine or placebo (total vaccinated cohort for safety analysis)

Solicited symptom	Type	Follow-up	p-values			
			HRV $10^{4.7}$ *versus* HRV $10^{5.2}$	HRV $10^{4.7}$ *versus* HRV $10^{5.8}$	HRV $10^{5.2}$ *versus* HRV $10^{5.8}$	Pooled HRV groups *versus* placebo
Cough/ runny nose	Any	Onset 15 days	0.942	0.941	0.883	0.113
	Any	Onset 8 days	0.689	0.946	0.640	0.247
	Related	Onset 8 days	0.639	0.737	0.947	0.956
	Grade 2 or 3	Onset 8 days	0.900	0.380	0.490	0.052
	Grade 3	Onset 8 days	0.638	0.638	1.000	0.085
Diarrhea	Any	Onset 15 days	0.512	0.475	0.171	0.080
	Any	Onset 8 days	0.910	0.386	0.327	0.217
	Related	Onset 8 days	0.899	0.537	0.715	0.688
	Grade 2 or 3	Onset 8 days	1.000	1.000	1.000	0.065
	Grade 3	Onset 8 days	0.234	0.328	1.000	0.369
Irritability/ fussiness	Any	Onset 15 days	0.365	0.195	0.755	0.229
	Any	Onset 8 days	0.381	0.306	0.941	0.224
	Related	Onset 8 days	0.951	0.543	0.503	1.000
	Grade 2 or 3	Onset 8 days	0.761	0.541	0.360	0.051
	Grade 3	Onset 8 days	0.682	0.743	1.000	0.351
Loss of appetite	Any	Onset 15 days	0.760	1.000	0.807	0.424
	Any	Onset 8 days	0.804	0.804	1.000	0.172
	Related	Onset 8 days	0.818	0.644	0.877	0.261
	Grade 2 or 3	Onset 8 days	0.393	0.622	0.178	0.250
	Grade 3	Onset 8 days	0.674	0.519	1.000	0.383
Fever	Any	Onset 15 days	0.468	0.723	0.280	0.213
	Any	Onset 8 days	1.000	0.336	0.372	0.190
	Related	Onset 8 days	0.324	0.460	0.853	0.880
	Grade 2 or 3	Onset 8 days	0.844	0.434	0.603	0.487
	Grade 3	Onset 8 days	0.579	0.707	1.000	0.880
Vomiting	Any	Onset 15 days	0.079	0.474	0.332	0.729
	Any	Onset 8 days	0.291	0.542	0.710	0.711
	Related	Onset 8 days	0.852	0.246	0.380	0.938
	Grade 2 or 3	Onset 8 days	0.036	0.399	0.247	0.742
	Grade 3	Onset 8 days	0.117	0.371	0.593	0.232

Notes: Onset 8 days = onset on Day 0 to Day 7 Onset 15 days = onset on Day 0 to Day 14
Any = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
p-value = results of comparison of percentage of subjects reporting the specified solicited symptom after any doses of HRV vaccine or placebo between groups by two-sided Fisher's exact test (significant level of $\alpha = 0.05$)

Supplement 46 to Supplement 51 present prevalence of diarrhea, vomiting and fever during the 15-day solicited follow-up period after each dose of HRV vaccine or placebo. For all groups, there was no specific day following either dose of HRV vaccine or placebo during which diarrhea or vomiting peaked. A peak in the incidence of fever was observed at Day 0 (day of vaccination) and Day 1 (day after vaccination) for all groups, and could be (at least) in part due to concomitantly administered routine vaccines (DTPw-HB+Hib) as confirmed by the placebo group.

Supplement 52 presents the duration (in days) of diarrhea, vomiting and fever during the solicited follow-up period. Values for mean duration of diarrhea, vomiting and fever during the 15-day solicited follow-up period after each dose of HRV vaccine or placebo were similar between the groups.

6.2.3 Unsolicited symptoms

Supplement 53 presents the percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms from Day 0 to Day 42 after any vaccination. The percentage of subjects reporting at least one unsolicited symptoms from Day 0 to Day 42 after vaccination were similar between the groups: 65.1% in the HRV $10^{4.7}$ group, 65.6% in the HRV $10^{5.2}$ group, 60.7% in the HRV $10^{5.8}$ group and 63.7% in the placebo group.

Table 24 presents the percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from Day 0 to Day 42 after any vaccination. Unsolicited symptoms reported by only six subjects (two subjects in the HRV $10^{4.7}$ group and four subjects in the placebo group), all from Brazil, were assessed as related to vaccination.

*Table 24: The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as **related** to vaccination, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)*

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV $10^{4.7}$ N = 538				HRV $10^{5.2}$ N = 540				HRV $10^{5.8}$ N = 540			
				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		2	0.4	0	1.3	0	0	0	0.7	0	0	0	0.7
Application site (1820)	Injection site reaction (0058)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
	Fever (0725)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7
	Pallor (0220)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
Respiratory system (1100)	Bronchitis (0805)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Comment: At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms

*Table 24 (continued): The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as **related** to vaccination, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)*

WHO Body System (CODE)	WHO Preferred term (CODE)	Pooled HRV groups N = 1618				Placebo N = 537			
				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL
At least one symptom		2	0.1	0	0.4	4	0.7	0.2	1.9
Application site (1820)	Injection site reaction (0058)	0	0	0	0.2	1	0.2	0	1
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.2	1	0.2	0	1
	Fever (0725)	1	0.1	0	0.3	0	0	0	0.7
	Pallor (0220)	0	0	0	0.2	1	0.2	0	1
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	0.2	1	0.2	0	1
Respiratory system (1100)	Bronchitis (0805)	1	0.1	0	0.3	0	0	0	0.7

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Comment: At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms

Table 25 presents the percentage of subjects with grade 3 unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination. The percentage of subjects with grade "3" unsolicited symptoms from Day 0 to Day 42 after vaccination were similar between the groups.

*Table 25: The percentage of subjects with **grade "3"** unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)*

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV $10^{4.7}$ N = 538				HRV $10^{5.2}$ N = 540				HRV $10^{5.8}$ N = 540			
				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		15	2.8	1.6	4.6	27	5	3.3	7.2	14	2.6	1.4	4.3
Application site (1820)	Dermatitis contact (0049)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7
	Allergic reaction (0712)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
	Death, nos (0722)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1
	Edema generalized (0400)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
	Fever (0725)	0	0	0	0.7	2	0.4	0	1.3	1	0.2	0	1
	Pallor (0220)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
Central and peripheral nervous system (410)	Fever convulsions (1357)	1	0.2	0	1	0	0	0	0.7	1	0.2	0	1
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7
Gastrointestinal system (600)	Abdominal pain (0268)	2	0.4	0	1.3	3	0.6	0.1	1.6	1	0.2	0	1
	Anorexia (0165)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7
	Constipation (0204)	0	0	0	0.7	1	0.2	0	1	1	0.2	0	1
	Gastroenteritis (0293)	3	0.6	0.1	1.6	5	0.9	0.3	2.1	1	0.2	0	1
	Gastrointestinal disorder nos (1262)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1
Psychiatric (500)	Nervousness (0188)	1	0.2	0	1	1	0.2	0	1	1	0.2	0	1
Resistance mechanism (1830)	Infection (0736)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7
	Moniliasis (0741)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7
Respiratory system (1100)	Asthma (1367)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7
	Bronchitis (0805)	2	0.4	0	1.3	4	0.7	0.2	1.9	0	0	0	0.7
	Pharyngitis (0523)	3	0.6	0.1	1.6	7	1.3	0.5	2.7	2	0.4	0	1.3
	Pneumonia (0528)	5	0.9	0.3	2.2	8	1.5	0.6	2.9	6	1.1	0.4	2.4

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

*Table 25 (continued): The percentage of subjects with **grade "3"** unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)*

WHO Body System (CODE)	WHO Preferred term (CODE)	Pooled HRV groups N = 1618				Placebo N = 537			
				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL
At least one symptom		56	3.5	2.6	4.5	17	3.2	1.9	5
Application site (1820)	Dermatitis contact (0049)	1	0.1	0	0.3	0	0	0	0.7
Body as a whole general (1810)	Abdomen enlarged (0711)	1	0.1	0	0.3	0	0	0	0.7
	Allergic reaction (0712)	0	0	0	0.2	1	0.2	0	1
	Death, nos (0722)	1	0.1	0	0.3	0	0	0	0.7
	Edema generalized (0400)	0	0	0	0.2	1	0.2	0	1
	Fever (0725)	3	0.2	0	0.5	0	0	0	0.7
	Pallor (0220)	0	0	0	0.2	1	0.2	0	1
Central and peripheral nervous system (410)	Fever convulsions (1357)	2	0.1	0	0.4	0	0	0	0.7
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.2	1	0.2	0	1
Gastrointestinal system (600)	Abdominal pain (0268)	6	0.4	0.1	0.8	0	0	0	0.7
	Anorexia (0165)	1	0.1	0	0.3	0	0	0	0.7
	Constipation (0204)	2	0.1	0	0.4	0	0	0	0.7
	Gastroenteritis (0293)	9	0.6	0.3	1.1	4	0.7	0.2	1.9
	Gastrointestinal disorder nos (1262)	1	0.1	0	0.3	1	0.2	0	1
Psychiatric (500)	Nervousness (0188)	3	0.2	0	0.5	0	0	0	0.7
Resistance mechanism (1830)	Infection (0736)	1	0.1	0	0.3	1	0.2	0	1
	Moniliasis (0741)	1	0.1	0	0.3	0	0	0	0.7
Respiratory system (1100)	Asthma (1367)	1	0.1	0	0.3	0	0	0	0.7
	Bronchitis (0805)	6	0.4	0.1	0.8	0	0	0	0.7
	Pharyngitis (0523)	12	0.7	0.4	1.3	2	0.4	0	1.3
	Pneumonia (0528)	19	1.2	0.7	1.8	6	1.1	0.4	2.4

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 54, Supplement 55 and Supplement 56 respectively present percentage of doses with all, related and grade 3 unsolicited symptoms from Day 0 to Day 42 after any vaccination.

Supplement 57 and Supplement 58 respectively present the percentage of subjects and doses respectively reporting gastrointestinal symptoms (WHO code 600) from Day 0 to Day 42 after any vaccination. The percentage of subjects and doses reporting any and grade "3" gastrointestinal symptoms (WHO code 600) from Day 0 to Day 42 after vaccination were low and similar between the groups. None of the gastrointestinal symptoms were assessed as related to vaccination.

6.2.4 Concomitant medications

Percentages of subjects who took medications during the study were similar between the groups. During the study (with start date between Dose 1 of HRV vaccine or placebo and visit at the end of the first efficacy follow-up period), 476 subjects (88.5%) in the HRV $10^{4.7}$ group, 480 subjects (88.9%) in the HRV $10^{5.2}$ group, 484 subjects (89.6%) in the HRV $10^{5.8}$ group and 488 subjects (90.9%) in the placebo group took at least one medication.

Table 26 presents the percentage of doses with at least one concomitant medication administered from Day 0 to Day 14 after vaccination, by type. Supplement 59 presents the percentage of overall doses and subjects with at least one concomitant medication administered from Day 0 to Day 14 after any vaccination, by type.

Concomitant medications were administered to 428 subjects (79.6%) in the HRV $10^{4.7}$ group, 446 subjects (82.6%) in the HRV $10^{5.2}$ group, 430 subjects (79.6%) in the HRV $10^{5.8}$ group and 446 subjects (83.1%) in the placebo group from Day 0 to Day 14 after vaccination. The majority of subjects in each group received antipyretics from Day 0 to Day 14 after vaccination and percentages of subjects who took antipyretics were similar between the groups. There was no increase in the percentage of subjects who took medications after Dose 2 as compared to Dose 1 of HRV vaccine or placebo.

Table 26: Percentage of doses with at least one concomitant medication administered from Day 0 to Day 14 after vaccination, by type (total vaccinated cohort for safety analysis)

	Dose 1											
	HRV $10^{4.7}$ (N=538)				HRV $10^{5.2}$ (N=540)				HRV $10^{5.8}$ (N=540)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL			LL	UL
Any medication	346	64.3	60.1	68.4	355	65.7	61.6	69.7	361	66.9	62.7	70.8
Any antipyretic	342	63.6	59.3	67.6	343	63.5	59.3	67.6	355	65.7	61.6	69.7
Prophylactic antipyretic	69	12.8	10.1	15.9	69	12.8	10.1	15.9	80	14.8	11.9	18.1
Any antibiotic	6	1.1	0.4	2.4	15	2.8	1.6	4.5	10	1.9	0.9	3.4

	Pooled HRV groups (N=1618)				Placebo (N=537)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL
Any medication	1062	65.6	63.3	68.0	382	71.1	67.1	74.9
Any antipyretic	1040	64.3	61.9	66.6	372	69.3	65.2	73.2
Prophylactic antipyretic	218	13.5	11.8	15.2	74	13.8	11.0	17.0
Any antibiotic	31	1.9	1.3	2.7	15	2.8	1.6	4.6

	Dose 2											
	HRV $10^{4.7}$ (N=510)				HRV $10^{5.2}$ (N=509)				HRV $10^{5.8}$ (N=515)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL			LL	UL
Any medication	306	60.0	55.6	64.3	329	64.6	60.3	68.8	302	58.6	54.3	62.9
Any antipyretic	298	58.4	54.0	62.7	321	63.1	58.7	67.3	292	56.7	52.3	61.0
Prophylactic antipyretic	55	10.8	8.2	13.8	65	12.8	10.0	16.0	50	9.7	7.3	12.6
Any antibiotic	19	3.7	2.3	5.8	28	5.5	3.7	7.9	16	3.1	1.8	5.0

	Pooled HRV groups (N=1534)				Placebo (N=522)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL				
Any medication	937	61.1	58.6	63.5	318	60.9	56.6	65.1
Any antipyretic	911	59.4	56.9	61.9	310	59.4	55.0	63.6
Prophylactic antipyretic	170	11.1	9.6	12.8	56	10.7	8.2	13.7
Any antibiotic	63	4.1	3.2	5.2	15	2.9	1.6	4.7

Notes: For each dose:
N = number of subjects having received the considered dose of HRV vaccine or placebo
n/% = number/percentage of subjects who started taking the specified concomitant medication at least once from Day 0 to Day 14 after the considered dose of HRV vaccine or placebo
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 60 and Supplement 61 present the percentage of subjects who took antipyretics by day, from Day 0 to Day 42, respectively after Dose 1 and Dose 2 of HRV vaccine or placebo. The percentage of subjects who took antipyretics peaked on Day 0 and Day 1 of each dose in all groups (HRV vaccine or placebo with concomitant DTPw-HB+Hib vaccine).

6.2.5 Reactogenicity analysis by country

Supplement 62 to Supplement 87 present reactogenicity results by country for the total vaccinated cohort.

For each country, the incidences of any symptoms (solicited or unsolicited) during the 15-day solicited follow-up period, including grade "3" and related symptoms, were similar between the groups.

Although some differences in incidence rates of specific solicited symptoms were observed between the countries, the incidence rates were similar between the HRV vaccine groups and the placebo within each country. Country-specific customs and practices could account for the observed differences between countries. Difference in incidence of solicited symptoms was marked for some solicited symptoms. For example, the incidence of irritability, a subjective symptom, was lower in Venezuela (65–72%) than in Brazil (89–93%) and in Mexico (86–92%). On the other hand, the incidence of fever, a symptom whose evaluation is quantitative, was similar between the countries. Incidences of symptoms assessed as related to vaccination were higher in Brazil and in Mexico than in Venezuela. Also, related unsolicited symptoms were reported only in Brazil. Since attribution of the relationship is done by the respective investigators, country-specific practices could again account for the observed differences.

Overall, results of the reactogenicity analyses by country were the same as the global reactogenicity analysis with the reactogenicity profile of each viral concentration of HRV vaccine similar to that of the placebo in terms of the incidences of solicited and unsolicited symptoms reported after vaccination.

6.2.6 Serious adverse events

Appendix: Serious Adverse Events presents a summary table for the SAEs reported until the end of the first efficacy follow-up period and the clinical narratives for all SAEs reported until the end of the first efficacy follow-up period.

Among the subjects planned to receive two doses of HRV vaccine or placebo, 220 subjects (52 in the HRV $10^{4.7}$ group, 55 in the HRV $10^{5.2}$ group, 49 in the HRV $10^{5.8}$ group and 64 in the placebo group) reported at least one SAE until the end of the first efficacy follow-up period.

All SAEs reported until the end of the first efficacy follow-up period among the subjects planned to receive two doses of HRV vaccine or placebo were assessed as not related to study vaccination (HRV vaccine or placebo) by the respective investigators.

6.2.6.1 SAEs assessed as possibly related to the concomitantly administered routine vaccination

One SAE was assessed as possibly related to the concomitantly administered routine vaccination by the respective investigator. Description of this SAE is given below:

- [redacted]

6.2.6.2 SAEs with fatal outcome

Three fatalities were reported during the study. All of the deaths were assessed as not related to vaccination by the respective investigators. Summary of these cases is presented below.

- [redacted]
- [redacted]

- [redacted]

6.2.6.3 IS

One IS case was reported during the study and was assessed as not related to the vaccination. Description of the IS case is given below:

- [redacted]

6.2.6.4 SAEs ongoing at the data lock point for analysis

Four SAEs (cerebral palsy in one subject, retarded psychomotor development in two subjects and anemia in one subject) were ongoing at the end of the first efficacy follow-up period. Three of the subjects (two with cerebral palsy and one with retarded psychomotor development) did not require hospitalization but the cases were reported as SAEs because they were considered medically important by the respective investigators. All four SAEs were assessed as not related to vaccination.

6.3 ATP cohort for safety analysis

The ATP cohort for safety analysis consisted of 1965 subjects (499 subjects in the $10^{4.7}$ ffu HRV vaccine group, 487 subjects in the $10^{5.2}$ ffu HRV vaccine group, 493 subjects in the $10^{5.8}$ ffu HRV vaccine group and 486 subjects the placebo group).

Supplement 88 to Supplement 98 present reactogenicity results for the ATP cohort.

The results of the ATP safety cohort analyses were consistent with those observed in the total vaccinated cohort analyses.

7 Analysis of immunogenicity in subjects planned to receive two doses of HRV vaccine or placebo

7.1 Data sets analyzed

Analysis of immunogenicity was performed on the ATP cohort (primary analysis) and the total vaccinated cohort. See Section 3.15.4 for definition of cohorts identified for analyses and Section 4.2.3 for description of eligibility for analyses.

7.2 ATP cohort for immunogenicity analysis

The ATP cohort for immunogenicity analysis consisted of 1526 subjects (395 subjects in the $10^{4.7}$ ffu HRV vaccine group, 377 subjects in the $10^{5.2}$ ffu HRV vaccine group, 381 subjects in the $10^{5.8}$ ffu HRV vaccine group and 373 subjects the placebo group).

7.2.1 Immunogenicity of the HRV vaccine

Anti-rotavirus IgA antibody GMCs and seropositivity rates at each sampling timepoint are presented in Table 27.

Seroconversion rates in the three vaccine groups were similar at each post-vaccination timepoint. A trend toward higher anti-rotavirus IgA antibody GMCs at two months after Dose 2 of HRV vaccine or placebo was observed in the $10^{5.8}$ ffu HRV vaccine group as compared to the other vaccine groups. At the end of the first efficacy follow-up period, persistence of anti-rotavirus IgA antibodies in terms of seropositivity rate and GMCs was similar in the three vaccine groups.

Table 27: Anti-rotavirus IgA antibody GMCs and seropositivity rates (ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 20 U/ml				GMC (U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	Pre	395	0	0.0	0.0	0.9	<20.0	-	-
	PI(M2)	146	57	39.0	31.1	47.5	27.0	21.5	33.9
	PII(M4)	142	86	60.6	52.0	68.7	54.0	40.9	71.2
	PII(M10)	377	275	72.9	68.2	77.4	78.9	66.7	93.2
HRV $10^{5.2}$	Pre	374	0	0.0	0.0	1.0	<20.0	-	-
	PI(M2)	127	48	37.8	29.3	46.8	23.9	19.1	30.0
	PII(M4)	125	78	62.4	53.3	70.9	52.1	39.7	68.3
	PII(M10)	359	273	76.0	71.3	80.4	85.0	72.1	100.2
HRV $10^{5.8}$	Pre	377	0	0.0	0.0	1.0	<20.0	-	-
	PI(M2)	132	57	43.2	34.6	52.1	32.2	24.8	41.8
	PII(M4)	124	81	65.3	56.3	73.6	70.7	51.9	96.3
	PII(M10)	354	273	77.1	72.4	81.4	81.8	70.1	95.6
Placebo	Pre	368	0	0.0	0.0	1.0	<20.0	-	-
	PI(M2)	139	3	2.2	0.4	6.2	<20.0	-	-
	PII(M4)	132	7	5.3	2.2	10.6	<20.0	-	-
	PII(M10)	360	149	41.4	36.3	46.7	43.2	35.4	52.8

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Pre = pre-vaccination
PI(M2) = blood sample taken two months after Dose 1 of HRV vaccine or placebo
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period
Comment: The seroconversion rate was the seropositivity rate at the post-vaccination sampling timepoint in subjects initially negative for RV (for the ATP cohort, at post Dose 1 and post Dose 2 time point, seroconversion rate = seropositivity rate).

Supplement 99 and Supplement 100 respectively present reverse cumulative distribution curves of anti-rotavirus IgA antibody concentrations in the HRV vaccine group two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Table 28 presents seroconversion rate on combined doses. Seroconversion rates on combined doses were similar in the three vaccine groups.

Table 28: Anti-rotavirus IgA antibody seroconversion rates on combined doses (ATP cohort for immunogenicity analysis)

Group	N	Seroconversion on combined Dose 1 and Dose 2 at Visit 3			
				95% CI	
		n	%	LL	UL
HRV $10^{4.7}$	145	89	61.4	52.9	69.3
HRV $10^{5.2}$	130	86	66.2	57.3	74.2
HRV $10^{5.8}$	127	85	66.9	58.0	75.0
Placebo	132	7	5.3	2.2	10.6

Notes: N = number of subjects with available anti-rotavirus IgA antibody results at Visit 3 and/or with seroconversion at Visit 2
n/% = number/percentage of subjects who seroconverted at Visit 2 or Visit 3
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

The anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies are presented in Table 29. Results show that the GMCs induced by the vaccine are lower than the GMCs induced by the natural infection in the placebo group.

Table 29: Anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies (ATP cohort for immunogenicity analysis)

Group	Timing		GMC (U/ml)		
			Value	95% CI	
		N		LL	UL
HRV $10^{4.7}$	PI(M2)	57	127.1	97.5	165.6
	PII(M4)	86	161.7	124.2	210.6
	PII(M10)	275	169.6	146.4	196.6
HRV $10^{5.2}$	PI(M2)	48	100.6	75.2	134.5
	PII(M4)	78	140.7	111.0	178.5
	PII(M10)	273	166.8	144.8	192.1
HRV $10^{5.8}$	PI(M2)	57	150.4	113.7	198.8
	PII(M4)	81	199.6	152.4	261.5
	PII(M10)	273	152.7	134.4	173.5
Placebo	PI(M2)	3	327.3	3.6	29783.1
	PII(M4)	7	464.9	81.0	2668.1
	PII(M10)	149	343.3	278.4	423.4

Notes: N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PI(M2) = blood sample taken two months after Dose 1 of HRV vaccine or placebo
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

7.2.2 Immunogenicity of the HRV vaccine in the stool analysis subset

Refer to Section 3.7.3 for definition of the stool analysis subset.

Anti-rotavirus IgA antibody GMCs and seropositivity rates at each sampling timepoint are presented in Table 30.

Seroconversion rates in the three vaccine groups were similar at each post-vaccination timepoint. A trend toward higher anti-rotavirus IgA antibody GMCs at two months after Dose 2 of HRV vaccine or placebo was observed in the $10^{5.8}$ ffu HRV vaccine group as compared to the other vaccine groups. At the end of the first efficacy follow-up period, persistence of anti-rotavirus IgA antibodies in terms of seropositivity rate and GMCs was similar in the three vaccine groups.

Table 30: Anti-rotavirus IgA antibody GMCs and seropositivity rate (stool analysis subset, ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 20 U/ml				GMC (U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	Pre	118	0	0.0	0.0	3.1	<20.0	-	-
	PI(M2)	104	44	42.3	32.7	52.4	30.3	22.8	40.3
	PII(M4)	104	65	62.5	52.5	71.8	57.3	41.3	79.7
	PII(M10)	106	82	77.4	68.2	84.9	104.1	75.2	144.3
HRV $10^{5.2}$	Pre	112	0	0.0	0.0	3.2	<20.0	-	-
	PI(M2)	94	33	35.1	25.5	45.6	21.7	17.0	27.8
	PII(M4)	96	58	60.4	49.9	70.3	51.9	37.9	71.2
	PII(M10)	97	67	69.1	58.9	78.1	70.7	51.1	97.8
HRV $10^{5.8}$	Pre	111	0	0.0	0.0	3.3	<20.0	-	-
	PI(M2)	97	42	43.3	33.3	53.7	33.7	24.5	46.3
	PII(M4)	93	59	63.4	52.8	73.2	65.8	46.0	94.2
	PII(M10)	92	66	71.7	61.4	80.6	81.7	58.4	114.2
Placebo	Pre	104	0	0.0	0.0	3.5	<20.0	-	-
	PI(M2)	105	0	0.0	0.0	3.5	<20.0	-	-
	PII(M4)	99	4	4.0	1.1	10.0	<20.0	-	-
	PII(M10)	97	39	40.2	30.4	50.7	44.0	29.5	65.5

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Pre = pre-vaccination
PI(M2) = blood sample taken two months after Dose 1 of HRV vaccine or placebo
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period
Comment: The seroconversion rate was the seropositivity rate at the post-vaccination sampling timepoint in subjects initially negative for RV (for the ATP cohort, at post Dose 1 and post Dose 2 time point, seroconversion rate = seropositivity rate).

Table 31 presents the number of subjects with vaccine virus in stool samples collected at pre-determined timepoints.

The percentages of vaccinees with RV shedding between Day 6 and Day 10 after Dose 1 of HRV vaccine or placebo ranged from 35.2% to 44.1% between the vaccine groups. RV shedding between Day 6 and Day 10 after Dose 1 of HRV vaccine or placebo tended to be higher in the $10^{5.8}$ ffu HRV vaccine group as compared to the other vaccine groups.

None of the stool samples collected on the day of Dose 2 of HRV vaccine or placebo (approximately 2 months after Dose 1 of HRV vaccine or placebo) were RV positive, except for a stool sample from one subject in the $10^{5.8}$ ffu HRV vaccine group.

The percentages of vaccinees with RV shedding between Day 6 and Day 10 after Dose 2 of HRV vaccine or placebo ranged from 11.5% to 21.3% between the vaccine groups.

The RV type was analysed for subjects in the placebo group who shed RV after vaccination. None of the placebo recipients in the ATP immunogenicity cohort shed RV, except one subject who shed wild-type G2 RV. Three more placebo recipients who were eliminated from the ATP cohort also shed RV: RV isolate from one subject was the G1 vaccine strain at Day 60 and RV isolate from two subjects were non vaccine strains (G9 and wild-type G1).

Table 31: Number of subjects with vaccine virus in stool samples collected at pre-determined timepoints (ATP cohort for immunogenicity analysis)

Group	Shedding Dose 1								
	Day 0 [Day –1 to Day 0]			[Day 1 to Day 5]			Day 7 [Day 6 to Day 10]		
	N	n	%	N	n	%	N	n	%
HRV $10^{4.7}$	110	0	0.0	1	0	0.0	105	38	36.2
HRV $10^{5.2}$	100	0	0.0	1	0	0.0	105	37	35.2
HRV $10^{5.8}$	103	0	0.0	3	0	0.0	102	45	44.1
Placebo	98	0	0.0	2	0	0.0	96	0	0.0

Group	Shedding Dose 1					
	[Day 11 to Day 12]			Day 60 [Day –2 to Day 0 of Dose 2]		
	N	n	%	N	n	%
HRV $10^{4.7}$	0	-	-	100	0	0.0
HRV $10^{5.2}$	1	0	0.0	93	0	0.0
HRV $10^{5.8}$	2	0	0.0	91	1	1.1
Placebo	0	-	-	96	0	0.0

Group	Shedding Dose 2								
	[Day 1 to Day 5]			Day 7 [Day 6 to Day 10]			[Day 11 to Day 15]		
	N	n	%	N	n	%	N	n	%
HRV $10^{4.7}$	6	0	0.0	87	10	11.5	5	0	0.0
HRV $10^{5.2}$	4	1	25.0	89	19	21.3	2	0	0.0
HRV $10^{5.8}$	6	1	16.7	91	15	16.5	4	0	0.0
Placebo	2	0	0.0	93	1	1.1	1	0	0.0

Notes: N = number of subject with available stool results at the specified time point
n/% = number/percentage of subjects with rotavirus in stool collected at the specified time point

Table 32 presents percentage of subjects with vaccine virus in stool samples collected at pre-determined time points on combined doses. There was a trend towards lower percentage of subjects in the $10^{4.7}$ ffu HRV vaccine group shedding vaccine virus.

Table 32: Percentage of subjects with vaccine virus in stool samples collected at pre-determined time points, on combined time points (ATP cohort for immunogenicity analysis)

Group	Shedding – combined timepoints				
	N	n	%	95%CI	
				L.L.	U.L.
HRV $10^{4.7}$	118	45	38.1	29.4	47.5
HRV $10^{5.2}$	115	52	45.2	35.9	54.8
HRV $10^{5.8}$	115	55	47.8	38.4	57.3
Placebo	109	1	0.9	0.0	5.0

Notes: N = number of subject with available stool results for at least one time point
n/% = number/percentage of subjects with rotavirus in at least one stool
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 33 presents the percentage of subjects with vaccine take after each dose of HRV vaccine or placebo. Refer to Section 3.15.8.1 for rules on calculating vaccine take. There was a trend towards higher percentage of subjects in the $10^{5.8}$ ffu HRV vaccine group with vaccine take.

Table 33: Percentage of subjects with vaccine take after each dose of HRV vaccine or placebo (ATP cohort for immunogenicity analysis)

Group	Vaccine take after Dose 1, at Visit 2					Vaccine take after Dose 2, at Visit 3				
				95%CI				%	95%CI	
	N	n	%	L.L.	U.L.	N	n	%	L.L.	U.L.
HRV $10^{4.7}$	105	51	48.6	38.7	58.5	104	66	63.5	53.4	72.7
HRV $10^{5.2}$	105	52	49.5	39.6	59.5	99	62	62.6	52.3	72.1
HRV $10^{5.8}$	108	62	57.4	47.5	66.9	97	67	69.1	58.9	78.1
Placebo	105	0	0.0	0.0	3.5	99	4	4.0	1.1	10.0

Notes: *Dose 1:*
N = number of subject with available anti-rotavirus IgA antibody results at Visit 2 or with vaccine virus* in stools collected from after Visit 1 to Visit 2
n/% = number/percentage of subjects who seroconverted at Visit 2 or with vaccine virus* in stools collected after Visit 1 to Visit 2
Dose 2 – Visit 3:
N = number of subject with available anti-rotavirus IgA antibody results at Visit 3 or with vaccine virus* in stools collected after Visit 2 to Visit 3
n/% = number/percentage of subjects who seroconverted at Visit 3 or with vaccine virus* in stools collected after Visit 2 to Visit 3
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Comment: *RV in stools collected at pre-determined time points or vaccine virus in stools collected in case of GE episode

Table 34 presents the percentage of subjects with vaccine take after combined doses. Refer to Section 3.15.8.1 for rules on calculating vaccine take. There was a trend towards lower vaccine take in the $10^{4.7}$ ffu HRV vaccine group.

Table 34: Percentage of subjects with vaccine take after combined doses (ATP cohort for immunogenicity analysis)

Group	Vaccine take on combined Doses 1 and 2, at Visit 3				
				95%CI	
	N	n	%	L.L.	U.L.
HRV $10^{4.7}$	107	69	64.5	54.6	73.5
HRV $10^{5.2}$	109	79	72.5	63.1	80.6
HRV $10^{5.8}$	106	80	75.5	66.2	83.3
Placebo	99	4	4.0	1.1	10.0

Notes: N = number of subjects with available anti-rotavirus IgA antibody result at Visit 3, or who seroconverted at Visit 2, or with vaccine virus* in stools collected after Visit 1 to Visit 3
n/% = number/percentage of subjects who seroconverted at Visit 2 or 3, or with vaccine virus* in stools collected after Visit 1 to Visit 3
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Comment: *RV in stools collected at pre-determined time points or vaccine virus in stools collected in case of GE episode

Table 35 presents the standardized asymptotic 95% CIs for the difference in vaccine take on combined doses 1 and 2 at two months after Dose 2 of HRV vaccine or placebo (at Visit 3) between HRV vaccine and placebo groups.

The lowest value of the lower limit of the standardized asymptotic 95% CI for the difference in the percentage of subjects with vaccine take on combined doses 1 and 2 at two months after Dose 2 of HRV vaccine or placebo (at Visit 3) between each HRV vaccine group and (minus) the placebo group was above 49% indicating that the vaccine take was significantly higher in the HRV vaccine groups as compared to the placebo group.

Table 35: Difference in percentage of subjects with vaccine take on combined doses 1 and 2 at two months after Dose 2 of HRV vaccine or placebo (at Visit 3) between each HRV vaccine and placebo groups (ATP cohort for immunogenicity analysis)

						Difference in vaccine take			
							Value	95 % CI	
Group	N	%	Group	N	%	Groups difference	(%)	L.L	U.L
HRV $10^{4.7}$	107	64.5	Placebo	99	4.0	HRV $10^{4.7}$ - Placebo	60.4	49.9	69.5
HRV $10^{5.2}$	109	72.5				HRV $10^{5.2}$ - Placebo	68.4	58.3	76.7
HRV $10^{5.8}$	106	75.5				HRV $10^{5.8}$- Placebo	71.4	61.3	79.4

Notes: N = number of subjects
% = percentage of subjects with vaccine take on combined Doses 1 and 2, at Visit 3
95% CI = standardized asymptotic Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

7.2.3 Impact of feeding on immunogenicity of HRV vaccine

Supplement 101 presents the results of the logistic regression analysis to determine the impact of feeding on the vaccine take at two months after Dose 2 of HRV vaccine or placebo, on combined doses 1 and 2. None of the pre-defined feeding criteria including type of food and timing of feeding with respect to HRV vaccine dose had a significant effect on the vaccine take (all p-values > 0.1). Therefore, vaccine take rates by feeding criteria were not tabulated.

7.2.4 Immunogenicity analysis by country

Supplement 102, Supplement 103 and Supplement 104 present anti-rotavirus IgA antibody GMCs and seroconversion rates by country. Country-specific variations in immune response were observed. At two months after Dose 2 of HRV vaccine or placebo, the seroconversion rate in the HRV vaccine groups ranged from 54.7–74.4% in Brazil, 50.0–70.6% in Mexico and 60.5–63.0% in Venezuela.

7.2.5 Immunogenicity of routine vaccinations (DTPw-HB+Hib and OPV)

For the ATP cohort for immunogenicity, the majority of subjects (> 98%) in each group received the DTPw-HB+Hib vaccine concomitantly with Dose 1 and Dose 2 of HRV vaccine or placebo. None of the subjects received OPV concomitantly with Dose 1 and Dose 2 of HRV vaccine or placebo. For subjects with available routine vaccination serology results at Visit 3, more than 93% of subjects in each group received two doses of DTPw-HB+Hib and OPV vaccines between Visit 1 and before Visit 3. For subjects with available routine vaccination serology results at the end of the first efficacy follow-up period, more than 94% of subjects in each group received three doses of DTPw-HB+Hib and OPV vaccines between Visit 1 and before the end of the first efficacy follow-up period.

For immunogenicity analyses of routine vaccines, the Study Month 4 (two months after Dose 2 of HRV vaccine or placebo) timepoint reflects the impact of two doses of HRV vaccine, as compared to placebo, on the immune responses of two doses of concomitantly administered routine DTPw-HB+Hib vaccine and two doses of OPV vaccine given separately from the study vaccines. Since the primary course of routine vaccines consists of three doses, the Study Month 10 (at the end of the first efficacy follow-up period) timepoint evaluates any effect of the HRV vaccine on the immunogenicity DTPw-HB+Hib and OPV vaccines after completion of the full routine vaccination course. It should be noted that the immunogenicity data at Study Month 10 are "persistence data" since antibody levels were not measured immediately after completion of the three-dose primary vaccination course of routine vaccines.

Analysis of immunogenicity of routine vaccinations for the ATP cohort was performed on the subset of subjects who had documented receipt of at least two doses of routine vaccines between Visit 1 and before the end of the first efficacy follow-up period.

Two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period, the majority of subjects had seroprotective levels of anti-tetanus, anti-HBs, anti-PRP (≥ 0.15 mcg/ml and ≥ 1 mcg/ml) and anti-poliovirus types 1, 2 and 3 antibodies. The seroprotection rates for anti-diphtheria antibodies ranged from 58.8% to 75.4% two months after Dose 2 of HRV vaccine or placebo and from 68.5% to 74.5% at the end of the first efficacy follow-up period. The seropositivity rates for anti-BPT antibodies ranged from 59.0% to 65.3% at two months after Dose 2 of HRV vaccine or placebo and from 70.1% to 80.1% at the end of the first efficacy follow-up period.

Antibody responses to all routine vaccine antigens at two months after Dose 2 of HRV vaccine or placebo in the three HRV vaccine groups were similar to those of the placebo (control) indicating that there appeared to be no impact of HRV vaccine on immunogenicity of OPV and concomitantly administered DTPw-HB+Hib vaccine, except for anti-diphtheria antibodies. There was a trend towards lower anti-diphtheria antibody seroprotection rates in the $10^{4.7}$ ffu and $10^{5.2}$ ffu HRV vaccine groups as compared to the placebo group at two months after Dose 2 of HRV vaccine or placebo, but rates were similar at the end of the first efficacy follow-up period.

Persistence data for antibodies to all routine vaccine antigens at end of the first efficacy follow-up period in the three HRV vaccine groups were similar to those of the placebo (control) indicating that there was no apparent effect of the HRV vaccine on the immunogenicity of routine vaccines after completion of the three-dose primary vaccination course.

Antibody responses to each of the routine vaccine antigens at each timepoint are presented hereafter. Results of exploratory inferential analysis for differences between each vaccine group and placebo and between the pooled HRV vaccine group and the placebo group with respect to immune response to concomitant vaccination at two months after Dose 2 of HRV vaccine or placebo and at the end of first efficacy follow up period are also presented. Conclusions can not be drawn from the inferential analyses since clinical limits for non-inferiority were not pre-defined.

Anti-diphtheria antibody response

Anti-diphtheria antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 36.

Table 36: Anti-diphtheria antibody GMCs and seroprotection rates (ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 0.1 IU/ml				GMC (IU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	146	94	64.4	56.0	72.1	0.204	0.164	0.253
	PII(M10)	164	115	70.1	62.5	77.0	0.189	0.161	0.223
HRV $10^{5.2}$	PII(M4)	136	80	58.8	50.1	67.2	0.183	0.146	0.230
	PII(M10)	149	102	68.5	60.3	75.8	0.186	0.156	0.221
HRV $10^{5.8}$	PII(M4)	130	98	75.4	67.1	82.5	0.247	0.199	0.307
	PII(M10)	142	100	70.4	62.2	77.8	0.188	0.157	0.224
Pooled HRV groups	PII(M4)	412	272	66.0	61.2	70.6	0.209	0.184	0.237
	PII(M10)	455	317	69.7	65.2	73.9	0.188	0.170	0.207
Placebo	PII(M4)	133	94	70.7	62.2	78.2	0.276	0.216	0.354
	PII(M10)	149	111	74.5	66.7	81.3	0.201	0.169	0.238

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

Supplement 113 and Supplement 114 respectively present the standardized asymptotic 95% CIs for the difference in anti-diphtheria antibody seroprotection rate between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 115 and Supplement 116 respectively present the 95% CIs for the ratio of anti-diphtheria antibody GMCs between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 117 and Supplement 118 respectively present reverse cumulative distribution curves of anti-diphtheria antibody concentrations two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Anti-tetanus antibody response

Anti-tetanus antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 37.

Table 37: Anti-tetanus antibody GMCs and seroprotection rates (ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 0.1 IU/ml				GMC (IU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	147	145	98.6	95.2	99.8	1.106	0.925	1.321
	PII(M10)	166	166	100	97.8	100.0	1.230	1.106	1.368
HRV $10^{5.2}$	PII(M4)	136	136	100	97.3	100.0	1.096	0.921	1.305
	PII(M10)	150	148	98.7	95.3	99.8	1.140	1.008	1.290
HRV $10^{5.8}$	PII(M4)	131	128	97.7	93.5	99.5	1.051	0.868	1.274
	PII(M10)	143	143	100	97.5	100.0	1.179	1.040	1.337
Pooled HRV groups	PII(M4)	414	409	98.8	97.2	99.6	1.085	0.978	1.204
	PII(M10)	459	457	99.6	98.4	99.9	1.184	1.107	1.267
Placebo	PII(M4)	134	133	99.3	95.9	100.0	1.160	0.960	1.403
	PII(M10)	149	149	100	97.6	100.0	1.121	0.992	1.266

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

Supplement 119 and Supplement 120 respectively present the standardized asymptotic 95% CIs for the difference in anti-tetanus antibody seroprotection rate between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 121 and Supplement 122 respectively present the 95% CIs for the ratio of anti-tetanus antibody GMCs between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 123 and Supplement 124 respectively present reverse cumulative distribution curves of anti-tetanus antibody concentrations two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Anti-BPT antibody response

Anti-BPT antibody GMCs and seropositivity rates at each sampling timepoint are presented in Table 38.

Table 38: Anti-BPT antibody GMCs and seropositivity rates (ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 15 EL.U/ml				GMC (EL.U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	144	94	65.3	56.9	73.0	19.4	17.0	22.2
	PII(M10)	165	124	75.2	67.8	81.5	22.5	20.1	25.2
HRV $10^{5.2}$	PII(M4)	134	79	59.0	50.1	67.4	18.5	16.0	21.3
	PII(M10)	151	121	80.1	72.9	86.2	25.2	22.1	28.7
HRV $10^{5.8}$	PII(M4)	131	84	64.1	55.3	72.3	18.4	16.1	21.0
	PII(M10)	144	101	70.1	62.0	77.5	22.2	19.3	25.5
Pooled HRV groups	PII(M4)	409	257	62.8	58.0	67.5	18.8	17.4	20.3
	PII(M10)	460	346	75.2	71.0	79.1	23.2	21.6	25.0
Placebo	PII(M4)	130	80	61.5	52.6	69.9	17.6	15.4	20.2
	PII(M10)	148	106	71.6	63.6	78.7	22.4	19.4	25.7

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered seropositivity level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

Supplement 125 and Supplement 126 respectively present the standardized asymptotic 95% CIs for the difference in anti-BPT antibody seropositivity rate between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 127 and Supplement 128 respectively present the 95% CIs for the ratio of anti-BPT antibody GMCs between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 129 and Supplement 130 respectively present reverse cumulative distribution curves of anti-BPT antibody concentrations two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Anti-HBs antibody response

Anti-HBs antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 39.

Table 39: Anti-HBs antibody GMCs and seroprotection rates (ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 10 mIU/ml				GMC (mIU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	147	145	98.6	95.2	99.8	550.607	447.434	677.569
	PII(M10)	165	157	95.2	90.7	97.9	212.673	171.244	264.126
HRV $10^{5.2}$	PII(M4)	136	134	98.5	94.8	99.8	595.706	470.668	753.960
	PII(M10)	150	145	96.7	92.4	98.9	214.367	174.033	264.050
HRV $10^{5.8}$	PII(M4)	134	130	97.0	92.5	99.2	515.918	407.055	653.895
	PII(M10)	143	140	97.9	94.0	99.6	199.973	162.194	246.553
Pooled HRV groups	PII(M4)	417	409	98.1	96.3	99.2	553.237	485.976	629.806
	PII(M10)	458	442	96.5	94.4	98.0	209.166	185.198	236.237
Placebo	PII(M4)	133	131	98.5	94.7	99.8	674.888	527.372	863.667
	PII(M10)	149	144	96.6	92.3	98.9	238.668	193.571	294.271

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

Supplement 131 and Supplement 132 respectively present the standardized asymptotic 95% CIs for the difference in anti-HBs antibody seroprotection rate between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 133 and Supplement 134 respectively present the 95% CIs for the ratio of anti-HBs antibody GMCs between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 135 and Supplement 136 respectively present reverse cumulative distribution curves of anti-HBs antibody concentrations two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Anti-PRP antibody response

Anti-PRP antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 40.

Table 40: Anti-PRP antibody GMCs and seroprotection rates (ATP cohort for immunogenicity analysis)

Group	Timing	N	≥ 0.15 mcg/ml				≥ 1 mcg/ml				GMC (mcg/ml)		
					95% CI		n	%	95% CI		Value	95% CI	
			n	%	LL	UL			LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	143	143	100	97.5	100	138	96.5	92.0	98.9	6.420	5.359	7.691
	PII(M10)	165	164	99.4	96.7	100	155	93.9	89.1	97.1	3.987	3.477	4.571
HRV $10^{5.2}$	PII(M4)	136	135	99.3	96.0	100	120	88.2	81.6	93.1	5.638	4.491	7.078
	PII(M10)	149	148	99.3	96.3	100	136	91.3	85.5	95.3	3.995	3.419	4.667
HRV $10^{5.8}$	PII(M4)	133	132	99.2	95.9	100	121	91.0	84.8	95.3	5.114	4.158	6.288
	PII(M10)	143	143	100	97.5	100	131	91.6	85.8	95.6	3.592	3.107	4.152
Pooled HRV groups	PII(M4)	412	410	99.5	98.3	99.9	379	92.0	88.9	94.4	5.715	5.080	6.429
	PII(M10)	457	455	99.6	98.4	99.9	422	92.3	89.5	94.6	3.861	3.552	4.198
Placebo	PII(M4)	131	130	99.2	95.8	100	117	89.3	82.7	94.0	5.083	4.072	6.344
	PII(M10)	149	149	100	97.6	100	141	94.6	89.7	97.7	3.842	3.314	4.454

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

Supplement 137 to Supplement 140 present the standardized asymptotic 95% CIs for the difference in anti-PRP antibody seroprotection rates (≥ 0.15 mcg/ml and ≥ 1 mcg/ml) between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 141 and Supplement 142 respectively present the 95% CIs for the ratio of anti-PRP antibody GMCs between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 143 and Supplement 144 respectively present reverse cumulative distribution curves of anti-PRP antibody concentrations two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Anti-poliovirus types 1, 2 and 3 antibody response

Anti-poliovirus types 1, 2 and 3 antibody GMTs and seroprotection rates at each sampling timepoint are presented in Table 41.

Table 41: Anti-poliovirus types 1, 2 and 3 antibody GMTs and seroprotection rates (ATP cohort for immunogenicity analysis)

Antibody	Group	Timing	N	≥ 1:8 dilution				GMT		
						95% CI		Value	95% CI	
				n	%	LL	UL		LL	UL
Anti-polio type 1	HRV $10^{4.7}$	PII(M4)	147	145	98.6	95.2	99.8	1546.9	1207.7	1981.3
		PII(M10)	156	155	99.4	96.5	100	802.1	662.2	971.7
	HRV $10^{5.2}$	PII(M4)	135	132	97.8	93.6	99.5	1120.1	852.6	1471.6
		PII(M10)	139	139	100	97.4	100	731.3	603.3	886.5
	HRV $10^{5.8}$	PII(M4)	133	131	98.5	94.7	99.8	1261.4	979.9	1623.7
		PII(M10)	134	134	100	97.3	100	714.8	574.8	889.0
	Pooled HRV groups	PII(M4)	415	408	98.3	96.6	99.3	1304.5	1125.0	1512.7
		PII(M10)	429	428	99.8	98.7	100	751.0	669.5	842.4
	Placebo	PII(M4)	130	129	99.2	95.8	100	1322.7	1039.4	1683.0
		PII(M10)	138	138	100	97.4	100	693.9	566.9	849.3
Anti-polio type 2	HRV $10^{4.7}$	PII(M4)	147	145	98.6	95.2	99.8	1138.6	913.3	1419.4
		PII(M10)	164	162	98.8	95.7	99.9	469.7	390.1	565.5
	HRV $10^{5.2}$	PII(M4)	135	134	99.3	95.9	100	1042.7	838.3	1297.0
		PII(M10)	147	147	100	97.5	100	472.6	404.9	551.5
	HRV $10^{5.8}$	PII(M4)	133	132	99.2	95.9	100	1346.2	1101.4	1645.3
		PII(M10)	140	140	100	97.4	100	523.6	445.3	615.7
	Pooled HRV groups	PII(M4)	415	411	99.0	97.6	99.7	1167.5	1032.4	1320.3
		PII(M10)	451	449	99.6	98.4	99.9	486.8	441.6	536.6
	Placebo	PII(M4)	130	129	99.2	95.8	100	1112.1	892.9	1385.1
		PII(M10)	148	147	99.3	96.3	100	438.7	372.5	516.6
Anti-polio type 3	HRV $10^{4.7}$	PII(M4)	147	128	87.1	80.6	92.0	184.1	137.9	245.7
		PII(M10)	164	151	92.1	86.8	95.7	131.1	105.6	162.7
	HRV $10^{5.2}$	PII(M4)	135	114	84.4	77.2	90.1	158.0	113.8	219.3
		PII(M10)	147	134	91.2	85.4	95.2	107.3	83.7	137.6
	HRV $10^{5.8}$	PII(M4)	133	119	89.5	83.0	94.1	181.1	135.2	242.5
		PII(M10)	140	133	95.0	90.0	98.0	130.9	104.8	163.5
	Pooled HRV groups	PII(M4)	415	361	87.0	83.4	90.1	174.2	146.5	207.2
		PII(M10)	451	418	92.7	89.9	94.9	122.8	107.6	140.0
	Placebo	PII(M4)	130	110	84.6	77.2	90.3	155.5	110.7	218.4
		PII(M10)	148	138	93.2	87.9	96.7	109.2	87.6	136.2

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with titer above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PII(M10) = blood sample taken at the end of the first efficacy period

Supplement 145 to Supplement 150 present the standardized asymptotic 95% CIs for the difference in anti-poliovirus types 1, 2 and 3 antibody seroprotection rates between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the efficacy follow-up period.

Supplement 151 to Supplement 156 respectively present the 95% CIs for the ratio of anti-poliovirus types 1, 2 and 3 antibody GMTs between each HRV vaccine group/pooled vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

Supplement 157 to Supplement 162 present reverse cumulative distribution curves of anti-poliovirus types 1, 2 and 3 antibody titers two months after Dose 2 of HRV vaccine or placebo and at the end of the first efficacy follow-up period.

7.3 Total vaccinated cohort for immunogenicity analysis

The total vaccinated cohort for immunogenicity analysis (subjects with serology results available) consisted of 2151 subjects (537 subjects in the $10^{4.7}$ ffu HRV vaccine group, 535 subjects in the $10^{5.2}$ ffu HRV vaccine group, 540 subjects in the $10^{5.8}$ ffu HRV vaccine group and 539 subjects the placebo group).

Supplement 105 to Supplement 112 present immunogenicity of the HRV vaccine for the total vaccinated cohort.

Supplement 163 to Supplement 167 present immunogenicity of the routine vaccinations for the total vaccinated cohort.

The results of the total vaccinated cohort analyses were consistent with those observed in the ATP cohort.

8 Exploratory evaluation of three doses of HRV vaccine or placebo

Due to the small number of subjects who received a third dose of HRV vaccine or placebo, the results obtained in this exploratory evaluation should be interpreted with caution.

8.1 Study population receiving three doses of HRV vaccine or placebo

8.1.1 Study dates

The first visit for the first subject enrolled as part of the subset receiving three doses of HRV vaccine or placebo took place on January 17, 2002. The data lock point for this final analysis was April 8, 2003 (the day on which the last subject completed the study visit at the end of the first efficacy follow-up period).

8.2 Subject eligibility and attrition from study

8.2.1 Number and distribution of subjects

All of the 121 subjects who comprised the subset to receive three doses of HRV vaccine or placebo were enrolled in Brazil.

8.2.2 Study completion and drop out

There were no drop outs until the end of the first efficacy follow-up period among the subset receiving three doses of HRV vaccine or placebo.

8.2.3 Eligibility for analysis

Exploratory analyses for the subset receiving three doses of HRV vaccine or placebo were performed only on the total vaccinated cohort. All of the 121 subjects enrolled to receive three doses of HRV vaccine or placebo were included in the total vaccinated cohort.

8.2.4 Compliance with protocol specified procedures

Written informed consent was obtained from parents/guardians of all subjects prior to entry in the study.

All subjects receiving three doses of HRV vaccine or placebo returned for the study visit at the end of the first efficacy follow-up period. Therefore compliance with study completion until end of the first efficacy follow-up period was 100%.

Compliance for reactogenicity reporting was 100%.

Regurgitation within 30 minutes was reported following 30 doses. None of these subjects were eliminated from analyses since only total vaccinated cohort analyses were performed for the subset receiving three doses of HRV vaccine or placebo.

Compliance for administration of routine DTPw-HB+Hib vaccine in the subset receiving three doses of HRV vaccine or placebo was as follows:

- In the total vaccinated cohort, all subjects received the DTPw-HB+Hib vaccine concomitantly with the first (except one in the HRV $10^{4.7}$ group), second and third doses of HRV vaccine or placebo. None of the subjects received OPV concomitantly with the first, second and third doses of HRV vaccine or placebo.

- In the total vaccinated cohort for subjects with available routine vaccination serology results at Visit 3, more than 90% of subjects in each group received two doses of DTPw-HB+Hib and OPV vaccines between Visit 1 and before Visit 3.
- In the total vaccinated cohort for subjects with available routine vaccination serology results at Visit 4, more than 96% of subjects in each group received three doses of DTPw-HB+Hib and OPV vaccines between Visit 1 and before the end of the first efficacy follow-up period.

8.3 Demographic characteristics of the total vaccinated cohort

Demographic characteristics for the total vaccinated cohort are summarized in Supplement 168. The mean age at the time of Dose 1 of HRV vaccine or placebo was 9.8 weeks (range 6–12 weeks). The mean age at the time of Dose 2 of HRV vaccine or placebo was 19.5 weeks (range 15–25 weeks). The mean age at the time of Dose 3 of HRV vaccine or placebo was 29.3 weeks (range 24–37 weeks). The demographic profile of the four groups was similar with respect to mean age, mean height and mean weight at the time of Dose 1 of HRV vaccine or placebo and race distribution. Observed differences in female to male ratio between the groups can be attributed to random chance and are not deemed clinically relevant.

It should be noted that subjects in the cohort receiving three doses of HRV vaccine or placebo were older than those in the cohort planned to receive two doses of HRV vaccine or placebo (See Section 4.3.1).

Supplement 169 presents the weight and height increases from Visit 1 to each of the subsequent visits by group. The mean increase in height and weight from Visit 1 to Visits 2, 3 and 4 was similar among the four groups.

Supplement 170 presents a summary of feeding criteria on the day of each study vaccination by group. The feeding profile (percentage of subjects who were fed with breast milk, infant formula or both) of the four groups was similar.

8.4 Exploratory analysis of efficacy

8.4.1 Data sets analyzed

Exploratory analysis of efficacy was performed only on the total vaccinated cohort. See Section 3.15.4 for definition of cohorts identified for analyses.

8.4.2 Total vaccinated cohort for efficacy analysis

The total vaccinated cohort for analysis of efficacy consisted of 121 subjects (31 subjects in the $10^{4.7}$ ffu HRV vaccine group, 30 subjects in the $10^{5.2}$ ffu HRV vaccine group, 30 subjects in the $10^{5.8}$ ffu HRV vaccine group and 30 subjects the placebo group).

8.4.2.1 Characterization of GE episodes reported during the first efficacy follow-up period

The first efficacy follow-up period started from two weeks after Dose 3 of HRV vaccine or placebo and ended at the visit at the end of the first efficacy follow-up period (when subjects reached approximately one year of age).

Table 42 presents the number and percentage of subjects who reported RV GE of any intensity during the first efficacy follow-up period. Table 43 presents the number and percentage of subjects who reported RV GE of severe intensity during the first efficacy follow-up period.

As seen from Table 42 and Table 43, the percentages of subjects reporting RV GE was lower in the pooled HRV vaccine groups and in each HRV vaccine group as compared to the placebo group. None of the subjects in the HRV vaccine groups reported severe RV GE while all RV GE cases in the placebo group were rated as severe.

Table 42: Percentage of subjects reporting any RV GE from 2 weeks after Dose 3 of HRV vaccine or placebo until end of the first efficacy follow-up period (total vaccinated cohort for efficacy analysis)

			n/N		
				95%CI	
Group	**N**	**n**	**%**	**LL**	**UL**
HRV $10^{4.7}$	31	1	3.2	0.1	16.7
HRV $10^{5.2}$	30	0	0.0	0.0	11.6
HRV $10^{5.8}$	30	0	0.0	0.0	11.6
Pooled HRV Groups	91	1	1.1	0.0	6.0
Placebo	30	5	16.7	5.6	34.7

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
% = percentage of subjects reporting at least one RV GE episode in each group
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 43: Percentage of subjects reporting severe RV GE from 2 weeks after Dose 3 of HRV vaccine or placebo until end of the first efficacy follow-up period (total vaccinated cohort for efficacy analysis)

			n/N		
				95%CI	
Group	**N**	**n**	**%**	**LL**	**UL**
HRV $10^{4.7}$	31	0	0.0	0.0	11.2
HRV $10^{5.2}$	30	0	0.0	0.0	11.6
HRV $10^{5.8}$	30	0	0.0	0.0	11.6
Pooled HRV Groups	91	0	0.0	0.0	4.0
Placebo	30	5	16.7	5.6	34.7

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

No concurrent pathogens were identified in RV GE cases occurring from two weeks after Dose 3 of HRV vaccine or placebo until the end of the efficacy follow-up period.

8.5 Analysis of safety

8.5.1 Data sets analyzed

Analysis of safety was performed only on the total vaccinated cohort. See Section 3.15.4 for description of analyses cohorts.

8.5.2 Total vaccinated cohort for safety analysis

The total vaccinated cohort for analysis of safety consisted of 121 subjects (31 subjects in the $10^{4.7}$ ffu HRV vaccine group, 30 subjects in the $10^{5.2}$ ffu HRV vaccine group, 30 subjects in the $10^{5.8}$ ffu HRV vaccine group and 30 subjects the placebo group).

All subjects who were planned to receive a third dose of HRV vaccine or placebo, received their three doses.

8.5.2.1 Overall incidence of symptoms

Table 44 presents the percentages of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15-day solicited follow-up period for all doses.

The incidences of symptoms (solicited or unsolicited) during the 15-day solicited follow-up period were high in all groups. All subjects reported symptoms (solicited or unsolicited) during the 15-day solicited follow-up period after Dose 1 of HRV vaccine or placebo. Incidences of symptoms (solicited or unsolicited) including those rated as grade "3" in intensity and those assessed as related to vaccination were similar between the groups.

Table 44: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15-day solicited follow-up period (total vaccinated cohort for safety analysis)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	HRV $10^{4.7}$	31	31	100	88.8	100
	HRV $10^{5.2}$	30	30	100	88.4	100
	HRV $10^{5.8}$	30	30	100	88.4	100
	Pooled HRV groups	91	91	100	96.0	100
	Placebo	30	30	100	88.4	100
Dose 2	HRV $10^{4.7}$	31	28	90.3	74.2	98.0
	HRV $10^{5.2}$	30	28	93.3	77.9	99.2
	HRV $10^{5.8}$	30	29	96.7	82.8	99.9
	Pooled HRV groups	91	85	93.4	86.2	97.5
	Placebo	30	29	96.7	82.8	99.9
Dose 3	HRV $10^{4.7}$	31	30	96.8	83.3	99.9
	HRV $10^{5.2}$	30	29	96.7	82.8	99.9
	HRV $10^{5.8}$	30	29	96.7	82.8	99.9
	Pooled HRV groups	91	88	96.7	90.7	99.3
	Placebo	30	28	93.3	77.9	99.2
Overall/dose	HRV $10^{4.7}$	93	89	95.7	89.4	98.8
	HRV $10^{5.2}$	90	87	96.7	90.6	99.3
	HRV $10^{5.8}$	90	88	97.8	92.2	99.7
	Pooled HRV groups	273	264	96.7	93.8	98.5
	Placebo	90	87	96.7	90.6	99.3
Overall/subject	HRV $10^{4.7}$	31	31	100	88.8	100
	HRV $10^{5.2}$	30	30	100	88.4	100
	HRV $10^{5.8}$	30	30	100	88.4	100
	Pooled HRV groups	91	91	100	96.0	100
	Placebo	30	30	100	88.4	100

Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For each dose:
N = number of subjects having received the considered dose of HRV vaccine or placebo
n/% = number/percentage of subjects reporting at least one symptom for the considered dose of HRV vaccine or placebo
For overall/dose:
N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject:
N= number of subjects having received at least one dose of HRV vaccine or placebo
n/%= number percentage of subjects reporting at least one symptom

Supplement 171 and Supplement 172 respectively present the percentage of doses and of subjects reporting grade "3" and related symptoms (solicited or unsolicited) during the 15-day solicited follow-up period.

8.5.2.2 Solicited signs and symptoms

Table 45, Table 46 and Table 47 present the percentage of subjects with specific solicited symptoms including those graded "2 or 3" in intensity, those graded "3" in intensity and those considered to be related to vaccination, during the 15-day solicited follow-up period after each dose of HRV vaccine or placebo.

Supplement 173 presents the percentage of doses and subjects reporting specific solicited symptoms including those graded "2 or 3" in intensity, those graded "3" in intensity and those considered to be related to vaccination, during the 15-day solicited follow-up period after any dose of HRV vaccine or placebo.

Cough/runny nose, fever and irritability were the most commonly reported solicited symptoms in all groups. Diarrhea was the least frequently reported solicited general symptom. Incidences were similar between the groups for each solicited symptom including those rated as grade "2 or 3" in intensity, those rated as grade "3" in intensity and those assessed as related to vaccination.

An additional dose of HRV vaccine or placebo or the higher age of the subjects in this cohort did not appear to impact on the reactogenicity profile of the HRV vaccine as compared to the placebo.

Table 45: Percentage of subjects with each solicited symptom including those graded "2 or 3", those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after ***Dose 1*** *of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Group		HRV $10^{4.7}$ N = 31				HRV $10^{5.2}$ N = 30				HRV $10^{5.8}$ N = 30			
		n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL
Cough/ runny nose	Total	18	58.1	39.1	75.5	22	73.3	54.1	87.7	21	70.0	50.6	85.3
	Grade 2 or 3	5	16.1	5.5	33.7	8	26.7	12.3	45.9	11	36.7	19.9	56.1
	Grade 3	1	3.2	0.1	16.7	1	3.3	0.1	17.2	3	10.0	2.1	26.5
	Related	12	38.7	21.8	57.8	16	53.3	34.3	71.7	8	26.7	12.3	45.9
Diarrhea	Total	7	22.6	9.6	41.1	6	20.0	7.7	38.6	7	23.3	9.9	42.3
	Grade 2 or 3	5	16.1	5.5	33.7	2	6.7	0.8	22.1	4	13.3	3.8	30.7
	Grade 3	3	9.7	2.0	25.8	0	0.0	0.0	11.6	0	0.0	0.0	11.6
	Related	6	19.4	7.5	37.5	5	16.7	5.6	34.7	4	13.3	3.8	30.7
Irritability/ fussiness	Total	28	90.3	74.2	98.0	27	90.0	73.5	97.9	27	90.0	73.5	97.9
	Grade 2 or 3	19	61.3	42.2	78.2	20	66.7	47.2	82.7	20	66.7	47.2	82.7
	Grade 3	3	9.7	2.0	25.8	4	13.3	3.8	30.7	2	6.7	0.8	22.1
	Related	26	83.9	66.3	94.5	26	86.7	69.3	96.2	26	86.7	69.3	96.2
Loss of appetite	Total	6	19.4	7.5	37.5	9	30.0	14.7	49.4	7	23.3	9.9	42.3
	Grade 2 or 3	3	9.7	2.0	25.8	2	6.7	0.8	22.1	1	3.3	0.1	17.2
	Grade 3	0	0.0	0.0	11.2	0	0.0	0.0	11.6	0	0.0	0.0	11.6
	Related	2	6.5	0.8	21.4	7	23.3	9.9	42.3	7	23.3	9.9	42.3
Fever	Total	24	77.4	58.9	90.4	21	70.0	50.6	85.3	23	76.7	57.7	90.1
	Grade 2 or 3	7	22.6	9.6	41.1	10	33.3	17.3	52.8	10	33.3	17.3	52.8
	Grade 3	1	3.2	0.1	16.7	0	0.0	0.0	11.6	0	0.0	0.0	11.6
	Related	23	74.2	55.4	88.1	18	60.0	40.6	77.3	22	73.3	54.1	87.7
Vomiting	Total	7	22.6	9.6	41.1	12	40.0	22.7	59.4	7	23.3	9.9	42.3
	Grade 2 or 3	4	12.9	3.6	29.8	6	20.0	7.7	38.6	2	6.7	0.8	22.1
	Grade 3	2	6.5	0.8	21.4	2	6.7	0.8	22.1	0	0.0	0.0	11.6
	Related	5	16.1	5.5	33.7	11	36.7	19.9	56.1	5	16.7	5.6	34.7

Notes: N = number of subjects having received Dose 1 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 1 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 45 (continued): Percentage of subjects with each solicited symptom including those graded "2 or 3", those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after ***Dose 1*** *of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Group		**Pooled HRV groups N = 91**				**Placebo N = 30**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
Cough/ runny nose	Total	61	67.0	56.4	76.5	23	76.7	57.7	90.1
	Grade 2 or 3	24	26.4	17.7	36.7	11	36.7	19.9	56.1
	Grade 3	5	5.5	1.8	12.4	1	3.3	0.1	17.2
	Related	36	39.6	29.5	50.4	11	36.7	19.9	56.1
Diarrhea	Total	20	22.0	14.0	31.9	4	13.3	3.8	30.7
	Grade 2 or 3	11	12.1	6.2	20.6	3	10.0	2.1	26.5
	Grade 3	3	3.3	0.7	9.3	1	3.3	0.1	17.2
	Related	15	16.5	9.5	25.7	3	10.0	2.1	26.5
Irritability/ fussiness	Total	82	90.1	82.1	95.4	25	83.3	65.3	94.4
	Grade 2 or 3	59	64.8	54.1	74.6	18	60.0	40.6	77.3
	Grade 3	9	9.9	4.6	17.9	5	16.7	5.6	34.7
	Related	78	85.7	76.8	92.2	22	73.3	54.1	87.7
Loss of appetite	Total	22	24.2	15.8	34.3	12	40.0	22.7	59.4
	Grade 2 or 3	6	6.6	2.5	13.8	8	26.7	12.3	45.9
	Grade 3	0	0.0	0.0	4.0	0	0.0	0.0	11.6
	Related	16	17.6	10.4	27.0	10	33.3	17.3	52.8
Fever	Total	68	74.7	64.5	83.3	18	60.0	40.6	77.3
	Grade 2 or 3	27	29.7	20.5	40.2	5	16.7	5.6	34.7
	Grade 3	1	1.1	0.0	6.0	0	0.0	0.0	11.6
	Related	63	69.2	58.7	78.5	16	53.3	34.3	71.7
Vomiting	Total	26	28.6	19.6	39.0	8	26.7	12.3	45.9
	Grade 2 or 3	12	13.2	7.0	21.9	6	20.0	7.7	38.6
	Grade 3	4	4.4	1.2	10.9	1	3.3	0.1	17.2
	Related	21	23.1	14.9	33.1	4	13.3	3.8	30.7

Notes: N = number of subjects having received Dose 1 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 1 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 46: Percentage of subjects with each solicited symptom including those graded "2 or 3", those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after ***Dose 2*** *of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Group		HRV $10^{4.7}$ N = 31				HRV $10^{5.2}$ N = 30				HRV $10^{5.8}$ N = 30			
		n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL
Cough/ runny nose	Total	22	71.0	52.0	85.8	25	83.3	65.3	94.4	27	90.0	73.5	97.9
	Grade 2 or 3	14	45.2	27.3	64.0	17	56.7	37.4	74.5	14	46.7	28.3	65.7
	Grade 3	4	12.9	3.6	29.8	7	23.3	9.9	42.3	1	3.3	0.1	17.2
	Related	8	25.8	11.9	44.6	8	26.7	12.3	45.9	14	46.7	28.3	65.7
Diarrhea	Total	3	9.7	2.0	25.8	2	6.7	0.8	22.1	5	16.7	5.6	34.7
	Grade 2 or 3	1	3.2	0.1	16.7	1	3.3	0.1	17.2	4	13.3	3.8	30.7
	Grade 3	0	0.0	0.0	11.2	0	0.0	0.0	11.6	0	0.0	0.0	11.6
	Related	2	6.5	0.8	21.4	2	6.7	0.8	22.1	4	13.3	3.8	30.7
Irritability/ fussiness	Total	18	58.1	39.1	75.5	17	56.7	37.4	74.5	15	50.0	31.3	68.7
	Grade 2 or 3	11	35.5	19.2	54.6	12	40.0	22.7	59.4	10	33.3	17.3	52.8
	Grade 3	3	9.7	2.0	25.8	2	6.7	0.8	22.1	2	6.7	0.8	22.1
	Related	17	54.8	36.0	72.7	15	50.0	31.3	68.7	14	46.7	28.3	65.7
Loss of appetite	Total	13	41.9	24.5	60.9	10	33.3	17.3	52.8	7	23.3	9.9	42.3
	Grade 2 or 3	2	6.5	0.8	21.4	5	16.7	5.6	34.7	4	13.3	3.8	30.7
	Grade 3	0	0.0	0.0	11.2	1	3.3	0.1	17.2	1	3.3	0.1	17.2
	Related	7	22.6	9.6	41.1	7	23.3	9.9	42.3	7	23.3	9.9	42.3
Fever	Total	20	64.5	45.4	80.8	13	43.3	25.5	62.6	15	50.0	31.3	68.7
	Grade 2 or 3	13	41.9	24.5	60.9	8	26.7	12.3	45.9	7	23.3	9.9	42.3
	Grade 3	2	6.5	0.8	21.4	2	6.7	0.8	22.1	1	3.3	0.1	17.2
	Related	20	64.5	45.4	80.8	12	40.0	22.7	59.4	13	43.3	25.5	62.6
Vomiting	Total	12	38.7	21.8	57.8	7	23.3	9.9	42.3	11	36.7	19.9	56.1
	Grade 2 or 3	5	16.1	5.5	33.7	4	13.3	3.8	30.7	5	16.7	5.6	34.7
	Grade 3	2	6.5	0.8	21.4	1	3.3	0.1	17.2	2	6.7	0.8	22.1
	Related	6	19.4	7.5	37.5	5	16.7	5.6	34.7	6	20.0	7.7	38.6

Notes: N = number of subjects having received Dose 2 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 2 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 46 (continued): Percentage of subjects with each solicited symptom including those graded "2 or 3", those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after ***Dose 2*** *of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Group		**Pooled HRV groups N = 91**				**Placebo N = 30**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
Cough/ runny nose	Total	74	81.3	71.8	88.7	23	76.7	57.7	90.1
	Grade 2 or 3	45	49.5	38.8	60.1	13	43.3	25.5	62.6
	Grade 3	12	13.2	7.0	21.9	3	10.0	2.1	26.5
	Related	30	33.0	23.5	43.6	14	46.7	28.3	65.7
Diarrhea	Total	10	11.0	5.4	19.3	7	23.3	9.9	42.3
	Grade 2 or 3	6	6.6	2.5	13.8	3	10.0	2.1	26.5
	Grade 3	0	0.0	0.0	4.0	1	3.3	0.1	17.2
	Related	8	8.8	3.9	16.6	6	20.0	7.7	38.6
Irritability/ fussiness	Total	50	54.9	44.2	65.4	17	56.7	37.4	74.5
	Grade 2 or 3	33	36.3	26.4	47.0	10	33.3	17.3	52.8
	Grade 3	7	7.7	3.1	15.2	1	3.3	0.1	17.2
	Related	46	50.5	39.9	61.2	15	50.0	31.3	68.7
Loss of appetite	Total	30	33.0	23.5	43.6	6	20.0	7.7	38.6
	Grade 2 or 3	11	12.1	6.2	20.6	3	10.0	2.1	26.5
	Grade 3	2	2.2	0.3	7.7	0	0.0	0.0	11.6
	Related	21	23.1	14.9	33.1	5	16.7	5.6	34.7
Fever	Total	48	52.7	42.0	63.3	11	36.7	19.9	56.1
	Grade 2 or 3	28	30.8	21.5	41.3	4	13.3	3.8	30.7
	Grade 3	5	5.5	1.8	12.4	0	0.0	0.0	11.6
	Related	45	49.5	38.8	60.1	9	30.0	14.7	49.4
Vomiting	Total	30	33.0	23.5	43.6	4	13.3	3.8	30.7
	Grade 2 or 3	14	15.4	8.7	24.5	1	3.3	0.1	17.2
	Grade 3	5	5.5	1.8	12.4	0	0.0	0.0	11.6
	Related	17	18.7	11.3	28.2	4	13.3	3.8	30.7

Notes: N = number of subjects having received Dose 2 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 2 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 47: Percentage of subjects with each solicited symptom including those graded "2 or 3", those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after ***Dose 3*** *of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Group		HRV $10^{4.7}$ N = 31				HRV $10^{5.2}$ N = 30				HRV $10^{5.8}$ N = 30			
		n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL
Cough/ runny nose	Total	24	77.4	58.9	90.4	25	83.3	65.3	94.4	24	80.0	61.4	92.3
	Grade 2 or 3	12	38.7	21.8	57.8	11	36.7	19.9	56.1	12	40.0	22.7	59.4
	Grade 3	3	9.7	2.0	25.8	4	13.3	3.8	30.7	2	6.7	0.8	22.1
	Related	10	32.3	16.7	51.4	9	30.0	14.7	49.4	11	36.7	19.9	56.1
Diarrhea	Total	6	19.4	7.5	37.5	3	10.0	2.1	26.5	7	23.3	9.9	42.3
	Grade 2 or 3	5	16.1	5.5	33.7	1	3.3	0.1	17.2	6	20.0	7.7	38.6
	Grade 3	4	12.9	3.6	29.8	1	3.3	0.1	17.2	3	10.0	2.1	26.5
	Related	4	12.9	3.6	29.8	1	3.3	0.1	17.2	6	20.0	7.7	38.6
Irritability/ fussiness	Total	17	54.8	36.0	72.7	13	43.3	25.5	62.6	19	63.3	43.9	80.1
	Grade 2 or 3	8	25.8	11.9	44.6	8	26.7	12.3	45.9	8	26.7	12.3	45.9
	Grade 3	3	9.7	2.0	25.8	1	3.3	0.1	17.2	2	6.7	0.8	22.1
	Related	16	51.6	33.1	69.8	10	33.3	17.3	52.8	16	53.3	34.3	71.7
Loss of appetite	Total	12	38.7	21.8	57.8	11	36.7	19.9	56.1	14	46.7	28.3	65.7
	Grade 2 or 3	7	22.6	9.6	41.1	5	16.7	5.6	34.7	6	20.0	7.7	38.6
	Grade 3	2	6.5	0.8	21.4	1	3.3	0.1	17.2	1	3.3	0.1	17.2
	Related	11	35.5	19.2	54.6	8	26.7	12.3	45.9	12	40.0	22.7	59.4
Fever	Total	17	54.8	36.0	72.7	15	50.0	31.3	68.7	14	46.7	28.3	65.7
	Grade 2 or 3	8	25.8	11.9	44.6	4	13.3	3.8	30.7	8	26.7	12.3	45.9
	Grade 3	0	0.0	0.0	11.2	0	0.0	0.0	11.6	2	6.7	0.8	22.1
	Related	15	48.4	30.2	66.9	13	43.3	25.5	62.6	13	43.3	25.5	62.6
Vomiting	Total	9	29.0	14.2	48.0	9	30.0	14.7	49.4	7	23.3	9.9	42.3
	Grade 2 or 3	5	16.1	5.5	33.7	4	13.3	3.8	30.7	3	10.0	2.1	26.5
	Grade 3	1	3.2	0.1	16.7	1	3.3	0.1	17.2	1	3.3	0.1	17.2
	Related	9	29.0	14.2	48.0	7	23.3	9.9	42.3	6	20.0	7.7	38.6

Notes: N = number of subjects having received Dose 3 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 3 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

*Table 47 (continued): Percentage of subjects with each solicited symptom including those graded "2 or 3", those graded "3" in intensity and those considered to be related to vaccination, during the 15-day follow-up period after **Dose 3** of HRV vaccine or placebo (total vaccinated cohort for safety analysis)*

Group		**Pooled HRV groups N = 91**				**Placebo N = 30**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
Cough/ runny nose	Total	73	80.2	70.6	87.8	18	60.0	40.6	77.3
	Grade 2 or 3	35	38.5	28.4	49.2	10	33.3	17.3	52.8
	Grade 3	9	9.9	4.6	17.9	2	6.7	0.8	22.1
	Related	30	33.0	23.5	43.6	10	33.3	17.3	52.8
Diarrhea	Total	16	17.6	10.4	27.0	5	16.7	5.6	34.7
	Grade 2 or 3	12	13.2	7.0	21.9	3	10.0	2.1	26.5
	Grade 3	8	8.8	3.9	16.6	0	0.0	0.0	11.6
	Related	11	12.1	6.2	20.6	3	10.0	2.1	26.5
Irritability/ fussiness	Total	49	53.8	43.1	64.4	20	66.7	47.2	82.7
	Grade 2 or 3	24	26.4	17.7	36.7	11	36.7	19.9	56.1
	Grade 3	6	6.6	2.5	13.8	1	3.3	0.1	17.2
	Related	42	46.2	35.6	56.9	18	60.0	40.6	77.3
Loss of appetite	Total	37	40.7	30.5	51.5	12	40.0	22.7	59.4
	Grade 2 or 3	18	19.8	12.2	29.4	5	16.7	5.6	34.7
	Grade 3	4	4.4	1.2	10.9	1	3.3	0.1	17.2
	Related	31	34.1	24.5	44.7	8	26.7	12.3	45.9
Fever	Total	46	50.5	39.9	61.2	17	56.7	37.4	74.5
	Grade 2 or 3	20	22.0	14.0	31.9	5	16.7	5.6	34.7
	Grade 3	2	2.2	0.3	7.7	1	3.3	0.1	17.2
	Related	41	45.1	34.6	55.8	15	50.0	31.3	68.7
Vomiting	Total	25	27.5	18.6	37.8	7	23.3	9.9	42.3
	Grade 2 or 3	12	13.2	7.0	21.9	5	16.7	5.6	34.7
	Grade 3	3	3.3	0.7	9.3	2	6.7	0.8	22.1
	Related	22	24.2	15.8	34.3	6	20.0	7.7	38.6

Notes: N = number of subjects having received Dose 3 of HRV vaccine or placebo
n/% = number/percentage of subjects reporting the specified symptom after Dose 3 of HRV vaccine or placebo
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

8.5.2.3 Unsolicited symptoms

Supplement 174 presents the percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms from Day 0 to Day 42 after any vaccination.

The percentage of subjects reporting at least one unsolicited symptoms from Day 0 to Day 42 after vaccination were similar between the groups: 90.3% in the HRV $10^{4.7}$ group, 96.7% in the HRV $10^{5.2}$ group, 100% in the HRV $10^{5.8}$ group and 100% in the placebo group.

Table 48 presents the percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from Day 0 to Day 42 after any vaccination. Only one unsolicited symptom reported by a subject in the placebo group was assessed as related to vaccination.

Table 48: The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV $10^{4.7}$ N = 31				HRV $10^{5.2}$ N = 30				HRV $10^{5.8}$ N = 30			
				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		0	0	0	11.2	0	0	0	11.6	0	0	0	11.6
Respiratory system (1100)	Pneumonia (0528)	0	0	0	11.2	0	0	0	11.6	0	0	0	11.6

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 48 (continued): The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)

WHO Body System (CODE)	WHO Preferred term (CODE)	Pooled HRV groups N = 91				Placebo N = 30			
				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL
At least one symptom		0	0	0	4	1	3.3	0.1	17.2
Respiratory system (1100)	Pneumonia (0528)	0	0	0	4	1	3.3	0.1	17.2

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 49 presents the percentage of subjects with grade 3 unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination. The percentage of subjects with grade "3" unsolicited symptoms from Day 0 to Day 42 after vaccination were similar between the groups.

Table 49: The percentage of subjects with grade 3 unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV $10^{4.7}$ N = 31				HRV $10^{5.2}$ N = 30				HRV $10^{5.8}$ N = 30			
				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		1	3.2	0.1	16.7	4	13.3	3.8	30.7	2	6.7	0.8	22.1
Gastrointestinal system (600)	Gastroenteritis (0293)	1	3.2	0.1	16.7	0	0	0	11.6	2	6.7	0.8	22.1
Respiratory system (1100)	Pneumonia (0528)	0	0	0	11.2	4	13.3	3.8	30.7	0	0	0	11.6

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Table 49 (continued): The percentage of subjects with grade 3 unsolicited symptoms classified by WHO Preferred Terms, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety analysis)

WHO Body System (CODE)	WHO Preferred term (CODE)	Pooled HRV groups N = 91				Placebo N = 30			
				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL
At least one symptom		7	7.7	3.1	15.2	4	13.3	3.8	30.7
Gastrointestinal system (600)	Gastroenteritis (0293)	3	3.3	0.7	9.3	3	10	2.1	26.5
Respiratory system (1100)	Pneumonia (0528)	4	4.4	1.2	10.9	1	3.3	0.1	17.2

Notes: N = number of subjects having received at least one dose of HRV vaccine or placebo
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 175, Supplement 176 and Supplement 177 respectively present percentage of doses with any, related and grade 3 unsolicited symptoms from Day 0 to Day 42 after any vaccination.

8.5.2.4 Concomitant medications

Table 50 presents the percentage of doses with at least one concomitant medication administered from Day 0 to Day 14 after each study vaccination, by type. Supplement 178 presents the same data for overall doses and by subjects.

Concomitant medications were administered to 25 subjects (80.6%) in the HRV $10^{4.7}$ group, 24 subjects (80%) in the HRV $10^{5.2}$ group, 29 subjects (96.7%) in the HRV $10^{5.8}$ group and 24 subjects (80%) in the placebo group from Day 0 to Day 14 after vaccination. The majority of subjects in each group received antipyretics from Day 0 to Day 14 after vaccination. The percentages of subjects who took antipyretics from Day 0 to Day 14 were similar between the groups. Administration of a third dose of HRV vaccine or placebo did not result in increase in the percentage of subjects who took medications.

Table 50: Percentage of doses with at least one concomitant medication administered from Day 0 to Day 14 after vaccination, by type (total vaccinated cohort for safety analysis)

	Dose 1											
	HRV $10^{4.7}$ (N=31)				**HRV $10^{5.2}$ (N=30)**				**HRV $10^{45.8}$ (N=30)**			
Type	**n**	**%**	**95% CI LL**	**95% CI UL**	**n**	**%**	**95% CI LL**	**95% CI UL**	**n**	**%**	**95% CI LL**	**95% CI UL**
Any medication	17	54.8	36.0	72.7	19	63.3	43.9	80.1	22	73.3	54.1	87.7
Any antipyretic	17	54.8	36.0	72.7	18	60.0	40.6	77.3	22	73.3	54.1	87.7
Prophylactic antipyretic	0	0.0	0.0	11.2	0	0.0	0.0	11.6	0	0.0	0.0	11.6
Any antibiotic	1	3.2	0.1	16.7	1	3.3	0.1	17.2	0	0.0	0.0	11.6

	Pooled HRV groups (N=91)				**Placebo (N=30)**			
Type	**n**	**%**	**95% CI LL**	**95% CI UL**	**n**	**%**	**95% CI LL**	**95% CI UL**
Any medication	58	63.7	53.0	73.6	17	56.7	37.4	74.5
Any antipyretic	57	62.6	51.9	72.6	17	56.7	37.4	74.5
Prophylactic antipyretic	0	0.0	0.0	4.0	0	0.0	0.0	11.6
Any antibiotic	2	2.2	0.3	7.7	0	0.0	0.0	11.6

	Dose 2											
	HRV $10^{4.7}$ (N=31)				**HRV $10^{5.2}$ (N=30)**				**HRV $10^{45.8}$ (N=30)**			
Type	**n**	**%**	**95% CI LL**	**95% CI UL**	**n**	**%**	**95% CI LL**	**95% CI UL**	**n**	**%**	**95% CI LL**	**95% CI UL**
Any medication	19	61.3	42.2	78.2	13	43.3	25.5	62.6	19	63.3	43.9	80.1
Any antipyretic	19	61.3	42.2	78.2	13	43.3	25.5	62.6	17	56.7	37.4	74.5
Prophylactic antipyretic	0	0.0	0.0	11.2	0	0.0	0.0	11.6	0	0.0	0.0	11.6
Any antibiotic	1	3.2	0.1	16.7	3	10.0	2.1	26.5	1	3.3	0.1	17.2

	Pooled HRV groups (N=91)				**Placebo (N=30)**			
Type	**n**	**%**	**95% CI LL**	**95% CI UL**	**n**	**%**	**95% CI LL**	**95% CI UL**
Any medication	51	56.0	45.2	66.4	15	50.0	31.3	68.7
Any antipyretic	49	53.8	43.1	64.4	14	46.7	28.3	65.7
Prophylactic antipyretic	0	0.0	0.0	4.0	1	3.3	0.1	17.2
Any antibiotic	5	5.5	1.8	12.4	2	6.7	0.8	22.1

Table 50 (continued): Percentage of doses with at least one concomitant medication administered from Day 0 to Day 14 after vaccination, by type (total vaccinated cohort for safety analysis)

	Dose 3											
	HRV $10^{4.7}$ (N=31)				HRV $10^{5.2}$ (N=30)				HRV $10^{45.8}$ (N=30)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL			LL	UL
Any medication	15	48.4	30.2	66.9	11	36.7	19.9	56.1	16	53.3	34.3	71.7
Any antipyretic	12	38.7	21.8	57.8	10	33.3	17.3	52.8	15	50.0	31.3	68.7
Prophylactic antipyretic	0	0.0	0.0	11.2	0	0.0	0.0	11.6	0	0.0	0.0	11.6
Any antibiotic	4	12.9	3.6	29.8	0	0.0	0.0	11.6	2	6.7	0.8	22.1

	Pooled HRV groups (N=91)				Placebo (N=30)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL
Any medication	42	46.2	35.6	56.9	14	46.7	28.3	65.7
Any antipyretic	37	40.7	30.5	51.5	14	46.7	28.3	65.7
Prophylactic antipyretic	0	0.0	0.0	4.0	0	0.0	0.0	11.6
Any antibiotic	6	6.6	2.5	13.8	1	3.3	0.1	17.2

Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For each dose:
N = number of subjects having received the considered dose of HRV vaccine or placebo
n/% = number/percentage of subjects who started taking the specified concomitant medication at least once from Day 0 to Day 14 after vaccination

8.5.3 Serious adverse events

Appendix: Serious Adverse Events presents a summary table for the SAEs reported until the end of the first efficacy follow-up period.

Among the subjects who received three doses of HRV vaccine or placebo, 27 subjects (6 in the HRV $10^{4.7}$ group, 6 in the HRV $10^{5.2}$ group, 8 in the HRV $10^{5.8}$ group and 7 in the placebo group) reported at least one SAE until the end of the first efficacy follow-up period. All subjects reporting SAEs recovered.

One SAE was assessed as possibly related to vaccination by the respective investigator. Description of the possibly related SAE is given below:

- [redacted]

There were no fatalities or IS in the subset receiving three doses of HRV vaccine or placebo.

8.6 Analysis of immunogenicity

8.6.1 Data sets analyzed

Analysis of immunogenicity was performed only on the total immunogenicity cohort. See Section 3.15.4 for definition of cohorts identified for analyses.

8.6.2 Total vaccinated cohort for immunogenicity analysis

The total vaccinated cohort for analysis of efficacy consisted of 121 subjects (31 subjects in the $10^{4.7}$ ffu HRV vaccine group, 30 subjects in the $10^{5.2}$ ffu HRV vaccine group, 30 subjects in the $10^{5.8}$ ffu HRV vaccine group and 30 subjects the placebo group).

8.6.2.1 Immunogenicity of GSK Biologicals' HRV vaccine

Anti-rotavirus IgA antibody GMCs and seropositivity rates at each sampling timepoint are presented in Table 51.

Seropositivity rates in the three vaccine groups at two months after Dose 2 of HRV vaccine or placebo and at two months after Dose 3 of HRV vaccine or placebo were similar. A trend toward higher anti-rotavirus IgA antibody GMCs at two months after Dose 2 of HRV vaccine or placebo and at two months after Dose 3 of HRV vaccine or placebo was observed in the $10^{5.8}$ ffu HRV vaccine group as compared to the other vaccine groups.

Table 51: Anti-rotavirus IgA antibody GMCs and seropositivity rates (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	≥20 U/ml				GMC (U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	Pre	31	1	3.2	0.1	16.7	<20.0	-	-
	PII(M4)	31	23	74.2	55.4	88.1	54.7	33.6	89.2
	PIII(M6)	31	27	87.1	70.2	96.4	83.3	51.3	135.0
HRV $10^{5.2}$	Pre	29	2	6.9	0.8	22.8	<20.0	-	-
	PII(M4)	29	18	62.1	42.3	79.3	58.6	31.8	108.0
	PIII(M6)	29	21	72.4	52.8	87.3	93.5	46.3	188.9
HRV $10^{5.8}$	Pre	30	1	3.3	0.1	17.2	<20.0	-	-
	PII(M4)	28	20	71.4	51.3	86.8	78.2	41.3	148.1
	PIII(M6)	30	25	83.3	65.3	94.4	128.7	73.8	224.4
Placebo	Pre	28	2	7.1	0.9	23.5	<20.0	-	-
	PII(M4)	28	4	14.3	4.0	32.7	<20.0	-	-
	PIII(M6)	30	8	26.7	12.3	45.9	27.1	13.5	54.4

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Pre = pre-vaccination
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Supplement 179 and Supplement 180 respectively present reverse cumulative distribution curves of anti-rotavirus IgA antibody concentrations in the HRV vaccine group two months after Dose 2 of HRV vaccine or placebo and two months after Dose 3 of HRV vaccine or placebo.

The anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies are presented in Table 52.

Table 52: Anti-rotavirus IgA antibody GMCs calculated on subjects seropositive for anti-rotavirus IgA antibodies (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	GMC (U/ml)		
			Value	95% CI	
				LL	UL
HRV $10^{4.7}$	Pre	1	30.0	-	-
	PII(M4)	23	98.8	64.1	152.4
	PIII(M6)	27	114.0	73.7	176.1
HRV $10^{5.2}$	Pre	2	162.8	-	-
	PII(M4)	18	172.9	105.5	283.3
	PIII(M6)	21	219.1	114.8	418.5
HRV $10^{5.8}$	Pre	1	396.0	-	-
	PII(M4)	20	177.9	103.0	307.5
	PIII(M6)	25	214.5	140.7	327.1
Placebo	Pre	2	519.3	-	-
	PII(M4)	4	201.8	10.8	3786.8
	PIII(M6)	8	419.9	105.5	1672.2

Notes: N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
Pre = pre-vaccination
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Table 53 presents the number of subjects with vaccine virus in stool samples collected at pre-determined timepoints.

None of the stool samples collected on the day of Dose 3 of HRV vaccine or placebo (approximately 2 months after Dose 2 of HRV vaccine or placebo) were RV positive, except for a stool sample from one subject in the placebo group.

The percentages of vaccinees with RV shedding at Day 7 after Dose 3 of HRV vaccine or placebo ranged from 7.1% to 10.7% between the vaccine groups.

Table 53: Number of subjects with vaccine virus in stool samples collected at pre-determined timepoints (total vaccinated cohort for immunogenicity analysis)

Group	Shedding Dose 3 [Day –1, Day 0]			Day 7 [Day 6 to Day 10]		
	N	n	%	N	n	%
HRV $10^{4.7}$	27	0	0.0	28	3	10.7
HRV $10^{5.2}$	25	0	0.0	28	2	7.1
HRV $10^{5.8}$	27	0	0.0	30	3	10.0
Placebo	26	1	3.8	30	1	3.3

Notes: N = number of subject with available stool results at the specified time point
n/% = number/percentage of subjects with rotavirus in stool collected at the specified time point

8.6.2.2 Immunogenicity of routine vaccinations (DTPw-HB+Hib and OPV)

Virtually all subjects received the DTPw-HB+Hib vaccine concomitantly with Dose 1, Dose 2 and Dose 3 of HRV vaccine or placebo. None of the subjects received OPV concomitantly with any dose of HRV vaccine or placebo. (refer to Section 8.2.4)

For immunogenicity analyses of concomitant vaccines, the Study Month 4 (two months after Dose 2 of HRV vaccine or placebo) timepoint explores the impact of two doses of HRV vaccine, as compared to placebo, on the immune responses of two doses of concomitantly administered routine DTPw-HB+Hib vaccine and two doses of OPV vaccine given separately from the study vaccines. The Study Month 6 (two months after Dose 3 of HRV vaccine or placebo) timepoint explores the impact of three doses of HRV vaccine, as compared to placebo, on the immune responses of three doses of concomitantly administered routine DTPw-HB+Hib vaccine and three doses of OPV vaccine given separately from the study vaccines. It should be noted that the immunogenicity data at Study Month 6 represents immunogenicity of the complete three-dose primary vaccination course of routine vaccines.

Two months after Dose 3 of HRV vaccine or placebo, the majority of subjects had seroprotective levels of anti-diphtheria, anti-tetanus, anti-HBs, anti-PRP (≥ 0.15 mcg/ml and ≥ 1 mcg/ml) and anti-poliovirus types 1, 2 and 3 antibodies and were seropositive for anti-BPT antibodies.

Antibody responses to all routine vaccine antigens at two months after Dose 2 of HRV vaccine or placebo and two months after Dose 3 of HRV vaccine or placebo (after completion of the primary vaccination course) in the three HRV vaccine groups were similar to those of the placebo (control) indicating that there that there appears to be no impact of HRV vaccine on immunogenicity of OPV and concomitantly administered DTPw-HB+Hib vaccine.

Antibody responses to each of the routine vaccine antigens at each timepoint are presented hereafter.

Anti-diphtheria antibody response

Anti-diphtheria antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 54. Supplement 181 presents reverse cumulative distribution curves of anti-diphtheria antibody concentrations two months after Dose 3 of HRV vaccine or placebo.

Table 54: Anti-diphtheria antibody GMCs and seroprotection rates (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	≥ 0.1 IU/ml				GMC (IU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	30	17	56.7	37.4	74.5	0.151	0.094	0.241
	PIII(M6)	31	26	83.9	66.3	94.5	0.501	0.291	0.863
HRV $10^{5.2}$	PII(M4)	30	17	56.7	37.4	74.5	0.149	0.090	0.246
	PIII(M6)	30	29	96.7	82.8	99.9	0.866	0.579	1.295
HRV $10^{5.8}$	PII(M4)	30	15	50.0	31.3	68.7	0.115	0.078	0.170
	PIII(M6)	30	29	96.7	82.8	99.9	0.772	0.520	1.145
Pooled HRV groups	PII(M4)	90	49	54.4	43.6	65.0	0.137	0.107	0.177
	PIII(M6)	91	84	92.3	84.8	96.9	0.692	0.535	0.895
Placebo	PII(M4)	27	16	59.3	38.8	77.6	0.185	0.106	0.323
	PIII(M6)	30	25	83.3	65.3	94.4	0.498	0.280	0.884

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Anti-tetanus antibody response

Anti-tetanus antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 55. Supplement 182 presents reverse cumulative distribution curves of anti-tetanus antibody concentrations two months after Dose 3 of HRV vaccine or placebo.

Table 55: Anti-tetanus antibody GMCs and seroprotection rates (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	≥ 0.1 IU/ml				GMC (IU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	31	31	100	88.8	100	1.215	0.878	1.681
	PIII(M6)	31	31	100	88.8	100	4.241	3.271	5.500
HRV $10^{5.2}$	PII(M4)	30	30	100	88.4	100	1.964	1.378	2.799
	PIII(M6)	30	30	100	88.4	100	5.397	4.173	6.980
HRV $10^{5.8}$	PII(M4)	30	30	100	88.4	100	1.725	1.270	2.343
	PIII(M6)	30	30	100	88.4	100	4.468	3.465	5.761
Pooled HRV groups	PII(M4)	91	91	100	96.0	100	1.598	1.325	1.927
	PIII(M6)	91	91	100	96.0	100	4.672	4.044	5.397
Placebo	PII(M4)	29	29	100	88.1	100	1.989	1.547	2.558
	PIII(M6)	30	30	100	88.4	100	3.647	2.871	4.633

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Anti-BPT antibody response

Anti-BPT antibody GMCs and seropositivity rates at each sampling timepoint are presented in Table 56. Supplement 183 presents reverse cumulative distribution curves of anti-BPT antibody concentrations two months after Dose 3 of HRV vaccine or placebo.

Table 56: Anti-BPT antibody GMCs and seropositivity rates (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	≥ 15 EL.U/ml				GMC (EL.U/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	31	27	87.1	70.2	96.4	25.2	19.8	32.1
	PIII(M6)	31	31	100	88.8	100	106.8	84.9	134.3
HRV $10^{5.2}$	PII(M4)	30	21	70.0	50.6	85.3	26.0	17.8	37.9
	PIII(M6)	30	30	100	88.4	100	104.6	76.7	142.6
HRV $10^{5.8}$	PII(M4)	30	23	76.7	57.7	90.1	24.9	18.6	33.3
	PIII(M6)	29	29	100	88.1	100	109.2	88.3	135.0
Pooled HRV groups	PII(M4)	91	71	78.0	68.1	86.0	25.4	21.4	30.1
	PIII(M6)	90	90	100	96.0	100	106.8	92.8	123.0
Placebo	PII(M4)	29	21	72.4	52.8	87.3	22.9	16.5	31.8
	PIII(M6)	30	30	100	88.4	100	82.0	60.3	111.5

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered level of seropositivity
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Anti-HBs antibody response

Anti-HBs antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 57. Supplement 184 presents reverse cumulative distribution curves of anti-HBs antibody concentrations two months after Dose 3 of HRV vaccine or placebo.

Table 57: Anti-HBs antibody GMCs and seroprotection rates (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	≥ 10 mIU/ml				GMC (mIU/ml)		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	31	29	93.5	78.6	99.2	389.386	203.756	744.133
	PIII(M6)	31	30	96.8	83.3	99.9	932.074	514.554	1688.38
HRV $10^{5.2}$	PII(M4)	30	29	96.7	82.8	99.9	736.301	412.463	1314.40
	PIII(M6)	30	30	100	88.4	100	1534.89	854.513	2756.98
HRV $10^{5.8}$	PII(M4)	30	30	100	88.4	100	796.338	478.171	1326.21
	PIII(M6)	30	30	100	88.4	100	1619.64	960.522	2731.05
Pooled HRV groups	PII(M4)	91	88	96.7	90.7	99.3	608.171	436.927	846.531
	PIII(M6)	91	90	98.9	94.0	100	1318.18	957.176	1815.35
Placebo	PII(M4)	29	29	100	88.1	100	650.523	426.515	992.183
	PIII(M6)	30	30	100	88.4	100	1139.23	733.341	1769.78

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Anti-PRP antibody response

Anti-PRP antibody GMCs and seroprotection rates at each sampling timepoint are presented in Table 58. Supplement 185 presents reverse cumulative distribution curves of anti-PRP antibody concentrations two months after Dose 3 of HRV vaccine or placebo.

Table 58: Anti-PRP antibody GMCs and seroprotection rates (total vaccinated cohort for immunogenicity analysis)

Group	Timing	N	≥ 0.15 mcg/ml				≥ 1 mcg/ml				GMC (mcg/ml)		
					95% CI		n	%	95% CI		Value	95% CI	
			n	%	LL	UL			LL	UL		LL	UL
HRV $10^{4.7}$	PII(M4)	28	28	100	87.7	100	26	92.9	76.5	99.1	5.795	3.606	9.315
	PIII(M6)	31	31	100	88.8	100	31	100	88.8	100	9.376	6.641	13.236
HRV $10^{5.2}$	PII(M4)	30	30	100	88.4	100	25	83.3	65.3	94.4	4.957	3.297	7.451
	PIII(M6)	30	30	100	88.4	100	30	100	88.4	100	8.598	6.326	11.686
HRV $10^{5.8}$	PII(M4)	30	30	100	88.4	100	30	100.0	88.4	100	7.534	5.569	10.193
	PIII(M6)	30	30	100	88.4	100	30	100	88.4	100	8.874	6.700	11.754
Pooled HRV groups	PII(M4)	88	88	100	95.9	100	81	92.0	84.3	96.7	6.009	4.806	7.513
	PIII(M6)	91	91	100	96.0	100	91	100	96.0	100	8.948	7.521	10.646
Placebo	PII(M4)	29	29	100	88.1	100	28	96.6	82.2	99.9	5.366	3.541	8.134
	PIII(M6)	30	30	100	88.4	100	29	96.7	82.8	99.9	7.456	5.383	10.327

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

Anti-poliovirus types 1, 2 and 3 antibody response

Anti-poliovirus types 1, 2 and 3 antibody GMTs and seroprotection rates at each sampling timepoint are presented in Table 59. Reverse cumulative distribution curves of anti-poliovirus types 1, 2 and 3 antibody titers two months after Dose 3 of HRV vaccine or placebo are presented in Supplement 186 to Supplement 188.

Table 59: Anti-poliovirus types 1, 2 and 3 antibody GMTs and seroprotection rates (total vaccinated cohort for immunogenicity analysis)

Antibody	Group	Timing	N	≥ 1:8 dilution				GMT		
						95% CI		Value	95% CI	
				n	%	LL	UL		LL	UL
Anti-polio 1	HRV $10^{4.7}$	PII(M4)	31	31	100	88.8	100	4005.4	2676.1	5994.8
		PIII(M6)	31	31	100	88.8	100	3238.8	2110.1	4971.1
	HRV $10^{5.2}$	PII(M4)	30	28	93.3	77.9	99.2	1888.9	925.5	3855.2
		PIII(M6)	30	30	100	88.4	100	2071.7	1444.8	2970.8
	HRV $10^{5.8}$	PII(M4)	30	29	96.7	82.8	99.9	1701.7	878.8	3295.2
		PIII(M6)	29	29	100	88.1	100	2148.2	1370.5	3367.2
	Pooled HRV groups	PII(M4)	91	88	96.7	90.7	99.3	2357.6	1670.5	3327.3
		PIII(M6)	90	90	100	96.0	100	2444.8	1935.3	3088.4
	Placebo	PII(M4)	29	28	96.6	82.2	99.9	1379.2	643.1	2957.6
		PIII(M6)	30	30	100	88.4	100	1335.6	784.9	2272.8
Anti-polio 2	HRV $10^{4.7}$	PII(M4)	31	31	100	88.8	100	2239.5	1506.4	3329.6
		PIII(M6)	31	31	100	88.8	100	1619.7	1066.2	2460.4
	HRV $10^{5.2}$	PII(M4)	30	28	93.3	77.9	99.2	831.6	414.1	1669.7
		PIII(M6)	30	30	100	88.4	100	1035.7	643.8	1665.9
	HRV $10^{5.8}$	PII(M4)	30	29	96.7	82.8	99.9	891.6	518.4	1533.2
		PIII(M6)	29	29	100	88.1	100	976.1	655.5	1453.6
	Pooled HRV groups	PII(M4)	91	88	96.7	90.7	99.3	1192.5	863.6	1646.5
		PIII(M6)	90	90	100	96.0	100	1185.3	928.2	1513.7
	Placebo	PII(M4)	29	28	96.6	82.2	99.9	1153.9	629.2	2116.2
		PIII(M6)	30	30	100	88.4	100	1415.0	886.9	2257.6
Anti-polio 3	HRV $10^{4.7}$	PII(M4)	31	23	74.2	55.4	88.1	84.7	39.6	181.2
		PIII(M6)	31	28	90.3	74.2	98.0	185.0	99.1	345.2
	HRV $10^{5.2}$	PII(M4)	30	19	63.3	43.9	80.1	55.0	23.2	130.4
		PIII(M6)	30	24	80.0	61.4	92.3	125.2	58.4	268.3
	HRV $10^{5.8}$	PII(M4)	30	16	53.3	34.3	71.7	45.3	18.3	112.1
		PIII(M6)	29	22	75.9	56.5	89.7	77.3	33.2	180.3
	Pooled HRV groups	PII(M4)	91	58	63.7	53.0	73.6	59.8	37.3	95.7
		PIII(M6)	90	74	82.2	72.7	89.5	122.6	80.6	186.6
	Placebo	PII(M4)	29	18	62.1	42.3	79.3	64.0	25.1	163.6
		PIII(M6)	30	26	86.7	69.3	96.2	174.8	88.3	346.0

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M4) = blood sample taken two months after Dose 2 of HRV vaccine or placebo
PIII(M6) = blood sample taken two months after Dose 3 of HRV vaccine or placebo

9 Discussion

This dose exploration study was conducted in Brazil, Mexico and Venezuela to assess the efficacy, reactogenicity, safety and immunogenicity of two doses of GSK Biologicals' live attenuated HRV vaccine belonging to the serotype G1P1A and genotype [P8]. A total of 2155 infants aged 6 to 12 weeks old were enrolled and randomized to receive two doses of one of three different virus concentrations ($10^{4.7}$, $10^{5.2}$ or $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine or placebo concomitantly with routine DTPw-HB+Hib vaccines.

The sample size in this study was large enough to reach a sufficient number of RV GE cases and demonstrate vaccine efficacy against any RV GE (primary endpoint), severe (≥ 11 points on a 20-point scale) RV GE and against hospitalization due to RV GE from two weeks after Dose 2 of HRV vaccine or placebo until end of the first efficacy follow-up period (at approximately one year of age).

A significant health burden exists worldwide due to mortality and morbidity in young children due to severe diarrhea and dehydration associated with RV GE. Prevention by vaccination is considered to be critical for effective control of RV disease. In this study, a statistically significant decrease (p-value < 0.05, two-sided Fisher's exact test) in the percentage of infants with any RV GE and severe RV from two weeks after Dose 2 of HRV vaccine or placebo until end of the first efficacy follow-up period was detected in pooled HRV vaccine groups and each HRV vaccine group as compared to the placebo group. The protective efficacy after two doses of HRV vaccine against RV GE of any severity ranged from 56% to 70%. The protective efficacy was even higher against severe RV GE (66% to 86%). There was a trend towards better efficacy in the $10^{5.8}$ ffu HRV vaccine group. Vaccine efficacy for the pooled HRV vaccine groups was 61.4% [95% CI, 42.3– 74.1] against any RV GE and 74.1% [95% CI, 55.8– 85] against severe RV GE. GSK Biologicals' HRV vaccine thus afforded protection against RV GE illness during the first year of life in susceptible children when severe disease is most common.

During the first efficacy follow-up period, the predominant RV types isolated were wild-type G1 (identified in 50.5% of RV GE episodes) and G9 (identified in 39.4% of RV GE episodes). In addition, G2, G3 and G4 types were also isolated. A statistically significant decrease (p-value < 0.05, two-sided Fisher's exact test) in the percentage of infants with severe RV GE caused by G1 and non-G1 serotypes was detected in pooled HRV vaccine groups as compared to the placebo group. For cases attributed to the wild-type G1 type, vaccine efficacy for the pooled HRV vaccine groups was 71.9% [95% CI, 50.3– 84.2] against any RV GE and 73.5% [95% CI, 41.2– 88.3] against severe RV GE. For cases attributed to the non-G1 types, vaccine efficacy for the pooled HRV vaccine groups was 49.4% [95% CI, 6.4– 72.1] against any RV GE and 73.1% [95% CI, 42.7– 87.7] against severe RV GE. Proof of concept that GSK Biologicals' monovalent G1[P8] HRV vaccine exhibits clinical protection against homologous and heterotypic strains was thus demonstrated in the Latin American setting where G1 and non-G1 serotypes were circulating.

In each country, a statistically significant decrease (p-value < 0.05, two-sided Fisher's exact test) in the percentage of infants with any and severe RV GE was detected in pooled HRV vaccine groups as compared to the placebo.

Efficacy of the HRV vaccine against any and severe RV GE was apparent from the day of Dose 1 onwards and this is an important parameter for public health considerations since efficacy was evident immediately after administration of the first dose.

A statistically significant decrease (p-value < 0.05, two-sided Fisher's exact test) in the percentage of infants hospitalized due to RV GE was detected in pooled HRV vaccine groups as compared to the placebo group. Vaccine efficacy for the pooled HRV vaccine groups was 79.0% [95% CI, 48.0– 92.0] against hospitalization due to RV GE. The vaccine efficacy against hospitalization was confirmed for the highest viral concentration. The data on vaccine efficacy against hospitalization for each viral concentration should be interpreted cautiously due to the limited number of hospitalization reported (9 in the pooled HRV vaccine groups and 14 in the placebo group).

Vaccine efficacy rates observed in this study (pooled HRV vaccine groups) against any and severe RV GE caused by homotypic G1 strains were similar to vaccine efficacy rates observed during a pilot efficacy trial with GSK Biologicals' HRV vaccine ($10^{4.7}$ ffu) in Finland ([10]) and efficacy of the parent 89-12 strain (10^5 ffu) in USA ([2]). The tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV) that was licensed in the USA in 1998 but then withdrawn in 1999 because of association with intussusception ([11], [12]) showed better efficacy in developed countries than in developing countries ([13], [14], [15], [16]). Efficacy of two doses of GSK Biologicals'

HRV vaccine (pooled HRV vaccine groups) compared favorably with the efficacy of three doses of RRV-TV (4 x 10^5 plaque forming units) in Venezuela ([15]). RRV-TV (4 x 10^4 plaque forming units) had only limited efficacy in Brazil ([17]). On the other hand, GSK Biologicals' HRV vaccine (pooled HRV vaccine groups) was efficacious against any and severe RV GE in all three countries (Brazil, Mexico and Venezuela).

Solicited and unsolicited symptoms were reported at similar frequencies in the HRV vaccine and placebo groups during the 15-day solicited follow-up period after each dose and there was no increase in reactogenicity from Dose 1 to Dose 2 or with increasing viral concentrations. In contrast, mild febrile reactions have been reported at a higher rate following administration of parent 89-12 strain ([2]) and RRV-TV ([5]) compared to placebo. When looking at the reactogenicity data by country, the incidence rates were similar between the HRV vaccine groups and the placebo within each country. The observed differences in reactogenicity between countries can be attributed to country-specific customs and practices.

GSK Biologicals' HRV vaccine elicited an immune response in terms of seroconversion for anti-rotavirus IgA antibodies in 60.6–65.3% of subjects two months after two doses of HRV vaccine. Persistence in terms of anti-rotavirus IgA antibody levels at approximately 8 months after Dose 2 of HRV vaccine was similar in the three HRV vaccine groups but IgA antibody levels were higher than at two months after Dose 2. This could most likely be due to natural RV infection. There was no significant increase in anti-rotavirus IgA antibody GMCs from Dose 1 to Dose 2 indicating catch-up effect (response to Dose 2 in subjects who were seronegative after Dose 1) rather than booster effect (significant increase in antibody concentrations after Dose 2 in subjects who were seropositive after Dose 1). RV shedding was seen mainly at Day 7 after the first dose with very little detectable HRV shedding observed 60 days after the first dose. There was a trend towards a better immunogenicity profile (in terms of IgA seroconversion rates, GMCs and vaccine take) in the $10^{5.8}$ ffu HRV vaccine group and immunogenicity observed in this group compared favourably with the parent 89-12 strain ([2]).

Anti-rotavirus IgA antibodies are considered as a strong marker of protection, though no correlate of protection against RV infection and disease has yet been identified ([18], [19]). Even though serological status of anti-rotavirus IgA antibodies two months after Dose 2 was known only for a subset of subjects, subjects in the pooled HRV vaccine groups who had seroconverted at two months post Dose 2 appeared less likely to develop RV GE during the first efficacy follow-up period: 11.2% (95% CI, 6.9–17.0) of seronegative subjects had RV GE *versus* 1.6% (95% CI, 0.5–3.7) of seropositive (seroconverted) subjects.

Immunogenicity of routine vaccines was evaluated two months after the second dose of HRV vaccine or placebo. Two months after the second dose, more than 58% of vaccinees had protective anti-diphtheria antibodies and more than 97% of subjects had protective anti-tetanus and anti-HBs antibodies. More than 99% of subjects had anti-PRP antibody level ≥ 0.15 mcg/ml and more than 88% had anti-PRP antibody level ≥ 1.0 mcg/ml. At least 84% of subjects had protective levels of neutralizing antibodies to each poliovirus serotypes. Seropositivity rate against anti-BPT antibodies were at least 59%. It should be noted that the complete routine vaccination course consists of three doses. Antibody responses (in terms of seroprotection/seropositivity rates and GMC/Ts) to all vaccine antigens contained in concomitantly administered routine DTPw-HB+Hib vaccine at two months after Dose 2 of HRV vaccine or placebo were similar between the three HRV vaccine groups and the placebo (control). Also, persistence at approximately one year of age in all HRV vaccine groups was similar to the placebo. Thus, there appeared to be no impact of HRV vaccine on immunogenicity of concomitantly administered routine vaccines. Also, there was no apparent impact of HRV vaccine on immunogenicity of OPV vaccine given separately from HRV vaccine with a two week interval as seen from similar serprotection rates to the three poliovirus serotypes between the three HRV vaccine groups and the placebo.

Administration of a third dose of GSK Biologicals' HRV vaccine or placebo was an exploratory evaluation. Due to the small number of subjects who received a third dose of HRV vaccine or placebo, the results obtained should be interpreted with caution. An additional dose or the higher age of the subjects in this cohort did not appear to impact on the reactogenicity profile of the HRV vaccine as compared to the placebo. There was a trend towards higher immunogenicity (in terms of anti-rotavirus IgA antibody GMCs) in the $10^{5.8}$ ffu HRV vaccine group two months after Dose 2 and Dose 3 of HRV vaccine. Seroprotection/seropositivity rates and GMC/Ts were high in all groups after completion of the three-dose primary vaccination course of routine DTPw-HB+Hib and OPV vaccines. There appeared to be no impact of HRV vaccine on immunogenicity of OPV and concomitantly administered DTPw-HB+Hib vaccine two months after the third dose of HRV vaccine or placebo.

10 Overall Conclusions

Study rota-006 demonstrated that two doses of GSK Biologicals' HRV vaccine were well tolerated, immunogenic and efficacious in protecting susceptible infants until approximately one year of age against RV GE in the Latin American setting where G1 and non-G1 RV serotypes were circulating. The highest viral concentration ($10^{5.8}$ ffu) evaluated showed higher immunogenicity and protection without increased reactogenicity.

Efficacy

- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups and each viral concentration) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of any RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The observed vaccine efficacy ranged between 55.7% to 70%. Thus, the primary objective of the study was met.

- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups and each viral concentration) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of severe RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The observed vaccine efficacy ranged between 65.8% to 85.6%.

- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of hospitalization due to RV GE relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. The observed vaccine efficacy in pooled HRV vaccine groups was 79%.

- Two doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups) given concomitantly to healthy infants with routine vaccinations effectively decreased the incidence of any and severe RV GE caused by G1 and non-G1 serotypes relative to the placebo during the period starting from 2 weeks after Dose 2 until the end of the first efficacy follow-up period. Proof of concept that GSK Biologicals' monovalent G1[P8] HRV vaccine exhibits clinical protection against homotypic and heterotypic strains was thus demonstrated in the Latin American setting where G1 and non-G1 serotypes were circulating.

- The highest viral concentration of GSK Biologicals' HRV vaccine evaluated, $10^{5.8}$ ffu, consistently performed better in terms of homotypic and heterotypic protection against any and severe RV GE.

Safety/Reactogenicity

- The safety and reactogenicity profile of two doses of each viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations was similar to that of the placebo in terms of the incidences of solicited/unsolicited symptoms and SAEs reported after vaccination. There was no increase in reactogenicity with the use of higher viral concentration and from Dose 1 to Dose 2.

- Even the highest viral concentration used, HRV vaccine at $10^{5.8}$ ffu, did not result in increased reactogenicity as compared to placebo, confirming the mild reactogenicity profile of GSK Biologicals' attenuated HRV vaccine.

Immunogenicity

- Vaccine take rates ranged from 48.6% to 57.4% at two months after the first dose of GSK Biologicals' HRV vaccine containing $10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu. Vaccine take rates ranged from 62.6% to 69.1% at two months after the second dose.

- Persistence in terms of serum anti-rotavirus IgA antibodies at the end of the first efficacy follow-up period (approximately 8 months after the second dose) was similar for the three viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine.

- RV shedding was observed predominantly after Dose 1 of GSK Biologicals' HRV vaccine with little residual shedding two months after Dose 1.

- There was a trend towards higher immunogenicity in terms of IgA seroconversion rates, GMCs and vaccine take in the $10^{5.8}$ ffu HRV vaccine group at two months after Dose 2.

- The effect of unrestricted feeding on the immunogenicity of GSK Biologicals' HRV vaccine was evaluated and indicated that none of the pre-defined feeding criteria had a significant effect.

- GSK Biologicals' HRV vaccine did not appear to impact on immunogenicity of routine vaccines, DTPw-HB and Hib (given concomitantly) or OPV vaccine.

Exploratory evaluation of three doses of HRV vaccine in a subset of subjects

- Within the limits of the small sample size, three doses of GSK Biologicals' HRV vaccine (pooled HRV vaccine groups and each viral concentration) given concomitantly to healthy infants with routine vaccinations appeared to decrease the incidence of any and severe RV GE relative to the placebo during the period starting from 2 weeks after Dose 3 until the end of the first efficacy follow-up period.

- The safety and reactogenicity profile of the three doses of each viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations was similar to that of the placebo in terms of the incidences of solicited/unsolicited symptoms and SAEs reported after vaccination.

- Anti-rotavirus IgA antibody responses in terms of seropositivity and GMCs were similar for the three viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) at two months after the second dose and at two months after the third dose of GSK Biologicals' HRV vaccine. There was a trend towards higher immunogenicity in the $10^{5.8}$ ffu HRV vaccine group.

- RV shedding observed after the third dose of GSK Biologicals' HRV vaccine was similar for the three viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu).

- GSK Biologicals' HRV vaccine did not appear to impact on immunogenicity of routine vaccines, DTPw-HB and Hib (given concomitantly) or OPV vaccine.

11 References

[1] Bernstein DI, Smith VE, Sherwood JR, Schiff GM, Sander DS, DeFeudis D, Spriggs DR, Ward RL. Safety and immunogenicity of a live attenuated human rotavirus 89-12 vaccine. Vaccine 1998;16:381–7.

[2] Bernstein DI, Sack DA, Rothstein E, Reisinger K, Smith VE, O'Sullivan D, Spriggs DR, Ward RL. Efficacy of live attenuated human rotavirus vaccine 89-12 in infants: a randomized placebo-controlled trial. Lancet 1999;354:287–90.

[3] White SJ and Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. Br J Cancer 1978;37:849–57.

[4] Ruuska T and Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for severity of diarrheal episodes. Scand J Infect Dis 1990;22:259–67.

[5] Joensuu J, Koskenniemi E, Pang X-L, Vesikari T. Randomized placebo-controlled trial of dose rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis. Lancet 1997;350:1205–9.

[6] Ward RL, Bernstein DI, Shukla R, *et al*. Effects of antibody to Rotavirus on protection of adults challenged with a human Rotavirus. J. Infect. Dis. 1989; 159:79–88.

[7] Melville-Smith M, Balfour A. Estimation of Corynebacterium diphtheria antitoxin in human sera: a comparison of an enzyme-linked immunosorbent assay with the toxin Neutralisation test. J Med Microbiol 1988; 24:279–83.

[8] Melville-Smith ME, Seagroatt VA, Watkins JT. A comparison of enzyme linked immunosorbent assay (ELISA) with the toxin Neutralisation test in mice as a method for the estimation of tetanus antitoxin in human sera. J Biol Stand 1983; 11:137–44.

[9] GSK Biologicals study rota-006, data on file.

[10] Efficacy evaluation of an oral human rotavirus (HRV) vaccine in previously uninfected Finnish infants. Poster presented at Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Diego, USA, Sep 27-30, 2002.

[11] American Academy of Pediatrics. Possible association of intussusception with rotavirus vaccination. Pediatrics 1999;104:575.

[12] CDC. Withdrawal of rotavirus vaccine recommendation. MMWR 1999;48:1007.

[13] Rennels MB, Glass RI, Dennehy PH, Bernstein DI, Pichichero ME, Zito ET. Safety and efficacy of high dose rhesus-human reassortant rotavirus vaccines – report of the National Multicenter Trial. Pediatrics 1996;97:7–13.

[14] Joensuu J, Koskenniemi E, Pang X-L, Vesikari T. Randomised placebo-controlled trial of rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis. Lancet 1997;350:1205 – 9.

[15] Perez-Schael I, Guntinas MJ, Perez M, Pagone V, Rojas A, Gonzales R, Cunto W, Hoshino Y, Kapikan AZ. Efficacy of the rhesus rotavirus-based quadrivalent vaccine in infants and young children in Venezuela. N Engl J Med. 1997;337:1181–7.

[16] Santosham M, Moulton LH, Reid R, Croll J, Weatherholt R, Ward R, Forro J, Zito E, Mack M, Brenneman G, Davidson BL. Efficacy and safety of high dose rhesus-human reassortant rotavirus vaccine in Native American population. J Pediatr 1997;131:632–8.

[17] Linhares Ac, Gabbay YB, Mascarenhas JDP *et al*. Immunogenicity, safety and efficacy of tetravalent rhesus-human, reassortant rotavirus vaccine in Belem, Brazil. Bull World Health Organ 1996;74:491–500.

[18] Ward RL. Mechanisms of protection against rotavirus in humans and mice. J Infect Dis 1996; 174 (Suppl 1);S51–8.

[19] Velaquez FR, Matson DO, Guerrero ML *et al*. Serum antibody as a marker of protection against natural rotavirus infection and disease. J Infect Dis 2000;182.

CONTENTS: SUPPLEMENTS

Supplement 1: Compliance (total vaccinated cohort for subset planned to receive two doses of study vaccine) 187
Supplement 2: Deviations from specifications for age and intervals between study visits (total vaccinated cohort for subset planned to receive two doses of study vaccine) 188
Supplement 3: Percentage of GE episodes with no available stools results from 2 weeks after Dose 2 up to the end of the first efficacy follow-up period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)..189
Supplement 4: Summary of demographic characteristics (age calculated in weeks) (total vaccinated cohort for subset planned to receive two doses of study vaccine) 190
Supplement 5: Summary of demographic characteristics (age calculated in weeks) in Brazil (total vaccinated cohort for subset planned to receive two doses of study vaccine) 191
Supplement 6: Summary of demographic characteristics (age calculated in weeks) in Mexico (total vaccinated cohort for subset planned to receive two doses of study vaccine) 192
Supplement 7: Summary of demographic characteristics (age calculated in weeks) in Venezuela (total vaccinated cohort for subset planned to receive two doses of study vaccine).....193
Supplement 8: Increase in height and weight from Visit 1 to Visit 2, 3 and 4 (total vaccinated cohort for subset planned to receive two doses of study vaccine) ...194
Supplement 9: Summary of demographic characteristics (age calculated in weeks) (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine).....195
Supplement 10: Percentage of subjects who received OPV at birth (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 196
Supplement 11: Summary of feeding criteria (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 196
Supplement 12: Duration (in years) of the follow-up period from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 197
Supplement 13: Percentage of subjects who reported GE episode(s) from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 198
Supplement 14: Characteristics of GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine).....199
Supplement 15: Characteristics of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 200
Supplement 16: Characteristics of RV GE episodes of G1 wild type, reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine).....201
Supplement 17: Characteristics of RV GE episodes of G9 type, reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 202

Supplement 18: Percentage of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period, by mixed infection (ATP cohort for efficacy for subset planned to receive two doses of study vaccine).....203
Supplement 19: Percentage of vaccinees reporting RV GE episodes from 2 weeks after Dose 2 up to the end of the first efficacy period, by status of anti-rotavirus IgA antibody concentration at two months after Dose 2 (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 203
Supplement 20: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (ATP cohort for efficacy for subset planned to receive two doses of study vaccine).....204
Supplement 21: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 205
Supplement 22: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (ATP cohort for efficacy for subset planned to receive two doses of study vaccine).....206
Supplement 23: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (ATP cohort for efficacy for subset planned to receive two doses of study vaccine) 207
Supplement 24: Duration (in years) of the follow-up period from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 208
Supplement 25: Percentage of subjects who reported GE episode(s) from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....209
Supplement 26: Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period, by severity (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 209
Supplement 27: Percentage of subjects with RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....210
Supplement 28: Characteristics of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 211
Supplement 29: Characteristics of RV GE episodes of G1 wild type, reported from 2 weeks after Dose 2 stools up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 212
Supplement 30: Characteristics of RV GE episodes of G9 type, reported from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....213
Supplement 31: Percentage of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period, by mixed infection (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....214

Supplement 32: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....215
Supplement 33: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 216
Supplement 34: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 217
Supplement 35: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....218
Supplement 36: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....219
Supplement 37: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....220
Supplement 38: Percentage of subjects hospitalized due to RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine) 221
Supplement 39: Percentage of vaccinees reporting RV GE episodes from 2 weeks after Dose 2 up to the end of the first efficacy period, by status of anti-rotavirus IgA antibody concentration at two months after Dose 2 (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine).....222
Supplement 40: Percentage of subjects who reported any or severe RV GE episode(s) from day of Dose 1 till Day 14 after Dose 2 (total vaccinated cohort for subset planned to receive two doses of study vaccine) 223
Supplement 41: Percentage of subjects who reported any or severe RV GE episode(s) other than vaccine strain and efficacy of the vaccine from day of Dose 1 till Day 14 after Dose 2 (total vaccinated cohort for subset planned to receive two doses of study vaccine) 224
Supplement 42: Percentage of subjects who reported any or severe RV GE episode(s) and efficacy of the vaccine from day of Dose 1 till the end of the first efficacy follow-up period (total vaccinated cohort for subset planned to receive two doses of study vaccine) 225
Supplement 43: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....226
Supplement 44: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15- day follow-up

period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 227
Supplement 45: Percentage of doses and subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 228
Supplement 46: Prevalence of diarrhea by day after vaccination, during the solicited 15-day follow-up period after Dose 1 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 232
Supplement 47: Prevalence of diarrhea by day after vaccination, during the solicited 15-day follow-up period after Dose 2 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 233
Supplement 48: Prevalence of fever by day after vaccination, during the solicited 15-day follow-up period after Dose 1 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 234
Supplement 49: Prevalence of fever by day after vaccination, during the solicited 15-day follow-up period after Dose 2 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 235
Supplement 50: Prevalence of vomiting by day after vaccination, during the solicited 15-day follow-up period after Dose 1 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 236
Supplement 51: Prevalence of vomiting by day after vaccination, during the solicited 15-day follow-up period after Dose 2 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 237
Supplement 52: Duration (in days) of diarrhea, vomiting and fever during the solicited 15-day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 238
Supplement 53: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 239
Supplement 54: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 243
Supplement 55: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 247
Supplement 56: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade “3” from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 248
Supplement 57: Percentage of subjects with gastrointestinal symptoms (unsolicited symptoms), from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 250
Supplement 58: Percentage of doses with gastrointestinal symptoms (unsolicited symptoms), from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 251

Supplement 59: Number and percentage of doses and of subjects who took at least one concomitant medication from Day 0 to Day 14 after vaccination by type (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....252
Supplement 60: Percentage of subjects who took antipyretics after Dose 1, by day from Day 0 to Day 42 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....253
Supplement 61: Percentage of subjects who took antipyretics after Dose 2, by day from Day 0 to Day 42 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....254
Supplement 62: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....255
Supplement 63: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....256
Supplement 64: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....257
Supplement 65: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....258
Supplement 66: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....259
Supplement 67: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....260
Supplement 68: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....261
Supplement 69: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....262
Supplement 70: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....263
Supplement 71: Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded “3” in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine).....264

Supplement 72: Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded “3” in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 272
Supplement 73: Percentage of doses and of subjects reporting each solicited general symptoms included those graded “3” in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)....280
Supplement 74: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 288
Supplement 75: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 292
Supplement 76: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 295
Supplement 77: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 297
Supplement 78: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 301
Supplement 79: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 303
Supplement 80: Percentage of subjects with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine y)....305
Supplement 81: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)....306
Supplement 82: Percentage of subjects with unsolicited symptoms classified by WHO preferred term with grade “3” from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 307
Supplement 83: Percentage of subjects with unsolicited symptoms classified by WHO preferred term with grade “3” from Day 0 to Day 42 after any vaccination in

Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 308
Supplement 84: Percentage of subjects with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 309
Supplement 85: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 310
Supplement 86: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 311
Supplement 87: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine) 312
Supplement 88: Number and percentage of subjects who received vaccine dose(s) (ATP cohort for safety for subset planned to receive two doses of study vaccine) 313
Supplement 89: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period (ATP cohort for safety for subset planned to receive two doses of study vaccine) 314
Supplement 90: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period (ATP cohort for safety for subset planned to receive two doses of study vaccine).....315
Supplement 91: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period (ATP cohort for safety for subset planned to receive two doses of study vaccine) 316
Supplement 92: Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine) 317
Supplement 93: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine).....325
Supplement 94: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine).....329
Supplement 95: Percentage of subjects with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine).....333
Supplement 96: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination from Day 0 to Day 42 after any

vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine).....334
Supplement 97: Percentage of subjects with grade "3" unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine) 335
Supplement 98: Percentage of doses with grade "3" unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine) 337
Supplement 99: Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations two months after Dose 2 (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 339
Supplement 100: Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 340
Supplement 101: Results of the exploratory logistic regression to assess impact of feeding criteria on the vaccine take (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 341
Supplement 102: Anti-rotavirus IgA antibody GMC and seroconversion rates in Brazil (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 341
Supplement 103: Anti-rotavirus IgA antibody GMC and seroconversion rates in Mexico (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 342
Supplement 104: Anti-rotavirus IgA antibody GMC and seroconversion rates in Venezuela (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 343
Supplement 105: Anti-rotavirus IgA antibody GMC and seroconversion rates (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine).....344
Supplement 106: Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 345
Supplement 107: Anti-rotavirus IgA antibody GMC and seroconversion rates in Brazil (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 346
Supplement 108: Anti-rotavirus IgA antibody GMC and seroconversion rates in Mexico (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine).....347
Supplement 109: Anti-rotavirus IgA antibody GMC and seroconversion rates in Venezuela (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine).....348
Supplement 110: Anti-rotavirus IgA antibody GMC and seroconversion rates for the stool subset (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine).....349
Supplement 111: Percentage of subjects with rotavirus in stool samples collected at pre-determined time points (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 350

Supplement 112: Percentage of subjects with rotavirus in stool samples collected at pre-determined time points, on combined time points (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 351
Supplement 113: Difference between pooled/each HRV vaccine groups and the placebo group in anti-diphtheria antibody seroprotection rates, at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 351
Supplement 114: Difference between pooled/each HRV vaccine groups and the placebo group in anti-diphtheria antibody seroprotection rates, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 351
Supplement 115: Ratio of anti-diphtheria antibody GMCs between pooled/each HRV vaccine groups and the placebo group, at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 352
Supplement 116: Ratio of anti-diphtheria antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 352
Supplement 117: Reverse cumulative curve for anti-diphtheria antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 353
Supplement 118: Reverse cumulative curve for anti-diphtheria antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 354
Supplement 119: Difference between pooled/each HRV vaccine groups and the placebo group in anti-tetanus antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 355
Supplement 120: Difference between pooled/each HRV vaccine groups and the placebo group in anti-tetanus antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 355
Supplement 121: Ratio of anti-tetanus antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 356
Supplement 122: Ratio of anti-tetanus antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 356
Supplement 123: Reverse cumulative curve for anti-tetanus antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 357
Supplement 124: Reverse cumulative curve for anti-tetanus antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 358

Supplement 125: Difference between pooled/each HRV vaccine groups and the placebo group in anti-BPT antibody seropositivity rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 359
Supplement 126: Difference between pooled/each HRV vaccine groups and the placebo group in anti-BPT seropositivity rates at the end of the first efficacy period (ATP cohort for immunogenicity) 359
Supplement 127: Ratio of anti-BPT antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 360
Supplement 128: Ratio of anti-BPT antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 360
Supplement 129: Reverse cumulative curve for anti-BPT antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 361
Supplement 130: Reverse cumulative curve for anti-BPT antibody concentrations at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 362
Supplement 131: Difference between pooled/each HRV vaccine groups and the placebo group in anti-HBs antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 363
Supplement 132: Difference between pooled/each HRV vaccine groups and the placebo group in anti-HBs antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 363
Supplement 133: Ratio of anti-HBs antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 364
Supplement 134: Ratio of anti-HBs antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 364
Supplement 135: Reverse cumulative curve for anti-HBs antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 365
Supplement 136: Reverse cumulative curve for anti-HBs antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 366
Supplement 137: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP concentrations ≥ 0.15 mcg/ml at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity) 367
Supplement 138: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP antibody concentrations ≥

1 mcg/ml at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)367
Supplement 139: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP antibody concentrations ≥ 0.15 mcg/ml at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 368
Supplement 140: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP antibody concentrations ≥ 1 mcg/ml ml at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 368
Supplement 141: Ratio of anti-PRP antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 369
Supplement 142: Ratio of anti-PRP antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 369
Supplement 143: Reverse cumulative curve for anti-PRP antibody concentrations, at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 370
Supplement 144: Reverse cumulative curve for anti-PRP antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 371
Supplement 145: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 1 antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 372
Supplement 146: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 2 antibody seroprotection at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 372
Supplement 147: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 3 antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 372
Supplement 148: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 1 antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 373
Supplement 149: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 2 antibody seroprotection at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 373
Supplement 150: Difference between pooled/ each HRV vaccine groups and the placebo group in anti-poliovirus type 3 antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 373

Supplement 151: Ratio of anti-poliovirus type 1 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 374
Supplement 152: Ratio of anti-poliovirus type 2 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 374
Supplement 153: Ratio of anti-poliovirus type 3 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 374
Supplement 154: Ratio of anti-poliovirus type 1 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 375
Supplement 155: Ratio of anti-poliovirus type 2 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 375
Supplement 156: Ratio of anti-poliovirus type 3 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 375
Supplement 157: Reverse cumulative curve for anti-poliovirus type 1 antibody titers at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 376
Supplement 158: Reverse cumulative curve for anti-poliovirus type 1 antibody titers at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 377
Supplement 159: Reverse cumulative curve for anti-poliovirus type 2 antibody titers at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 378
Supplement 160: Reverse cumulative curve for anti-poliovirus type 2 antibody titers at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 379
Supplement 161: Reverse cumulative curve for anti-poliovirus type 3 antibody titers at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 380
Supplement 162: Reverse cumulative curve for anti-poliovirus type 3 antibody titers at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine) 381
Supplement 163: Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 382
Supplement 164: Seropositivity rates and anti-BPT antibody GMCs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 383

Supplement 165: Seroprotection rates and anti-HBs antibody GMCs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 384
Supplement 166: Seroprotection rates and anti-PRP antibody GMCs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 385
Supplement 167: Seroprotection rates and anti-poliovirus types 1, 2 and 3 GMTs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine) 386
Supplement 168: Summary of demographic characteristics (age calculated in weeks) (total vaccinated cohort receiving three doses of study vaccine)....387
Supplement 169: Increase in height and weight from Visit 1 to Visit 2, 3, 4 and 5 (total vaccinated cohort receiving three doses of study vaccine)....388
Supplement 170: Summary of feeding criteria (total vaccinated cohort receiving three doses of study vaccine) 389
Supplement 171: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine) 390
Supplement 172: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up (total vaccinated cohort for safety receiving three doses of study vaccine) 391
Supplement 173: Percentage of doses and of subjects reporting each solicited general symptoms included those graded “3” and grade “2” or “3” in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine) 392
Supplement 174: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine) 396
Supplement 175: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine) 399
Supplement 176: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine) 402
Supplement 177: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade “3” from day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine) 403
Supplement 178: Number and percentage of doses and subjects who took at least one concomitant medication from Day 0 to Day 14 after vaccination by type (total vaccinated cohort for safety receiving three doses of study vaccine) 404
Supplement 179: Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations two months after Dose 2 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)....405
Supplement 180: Reverse cumulative curves for anti-rotavirus IgA antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine) 406

Supplement 181: Reverse cumulative curves for anti-diphtheria antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine) 407
Supplement 182: Reverse cumulative curves for anti-tetanus antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....408
Supplement 183: Reverse cumulative curves for anti-BPT antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....409
Supplement 184: Reverse cumulative curves for anti-HBs antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....410
Supplement 185: Reverse cumulative curves for anti-PRP antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....411
Supplement 186: Reverse cumulative curves for anti-poliovirus type 1 antibody titers two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....412
Supplement 187: Reverse cumulative curves for anti-poliovirus type 2 antibody titers two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....413
Supplement 188: Reverse cumulative curves for anti-poliovirus type 3 antibody titers two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine).....414

Supplement 1: Compliance (total vaccinated cohort for subset planned to receive two doses of study vaccine)

Dose	Group	Number of Doses	Doses NOT according to protocol	Number of general SS	Compliance % general
1	HRV_4.7	538	8	528	98.1
	HRV_5.2	540	10	528	97.8
	HRV_5.8	540	10	529	98.0
	Pooled HRV groups	1618	28	1585	98.0
	Placebo	537	16	532	99.1
2	HRV_4.7	510	13	506	99.2
	HRV_5.2	509	19	508	99.8
	HRV_5.8	515	10	512	99.4
	Pooled HRV groups	1534	42	1526	99.5
	Placebo	522	14	517	99.0
Total	HRV_4.7	1048	21	1034	98.7
	HRV_5.2	1049	29	1036	98.8
	HRV_5.8	1055	20	1041	98.7
	Pooled HRV groups	3152	70	3111	98.7
	Placebo	1059	30	1049	99.1

Notes: SS = Symptom sheet
Doses not according to protocol = number of doses with regurgitation

Supplement 2: Deviations from specifications for age and intervals between study visits (total vaccinated cohort for subset planned to receive two doses of study vaccine)

Group	Age	VAC_1-VAC_2	VIS_2-BL_3	VIS_3-BL_4
	Protocol	Protocol	Protocol	Protocol
	from 6 to 12 W	from 49 to 83 D	from 49 to 83 D	from 160 to 200 D
HRV_4.7	/	n = 21 subjects (from -1 to 34 D) 4.1% of 510 (28 subjects with empty value)	n = 23 subjects (from -18 to 28 D) 12.2% of 188 (350 subjects with empty value)	n = 7 subjects (from -26 to 139 D) 1.4% of 492 (46 subjects with empty value)
HRV_5.2	/	n = 32 subjects (from -3 to 36 D) 6.3% of 509 (31 subjects with empty value)	n = 15 subjects (from -17 to 36 D) 8.3% of 181 (359 subjects with empty value)	n = 13 subjects (from -11 to 40 D) 2.6% of 493 (47 subjects with empty value)
HRV_5.8	/	n = 35 subjects (from -1 to 37 D) 6.8% of 515 (25 subjects with empty value)	n = 20 subjects (from -7 to 23 D) 10.8% of 185 (355 subjects with empty value)	n = 10 subjects (from -63 to 37 D) 2.0% of 491 (49 subjects with empty value)
Placebo	/	n = 37 subjects (from -1 to 44 D) 7.1% of 522 (15 subjects with empty value)	n = 20 subjects (from -8 to 24 D) 10.7% of 187 (350 subjects with empty value)	n = 7 subjects (from -8 to 115 D) 1.4% of 500 (37 subjects with empty value)

Notes: W = Weeks D = days
n = number of subjects out of the specified interval
% = proportion of subjects out of the specified interval among with subjects present at the considered visits
% (for age) = proportion of subjects out of the specified interval using as denominator the number of subjects in the considered cohort.
VAC_1 = visit for first dose VAC_2 = visit for second dose
BL_3 = visit for post-vaccination blood sampling at 2 months after the second dose of HRV vaccine or placebo
BL_4 = visit for post-vaccination blood sampling at the end of the first efficacy follow-up period
VIS_2 = second visit VIS_3 = third visit

Supplement 3: Percentage of GE episodes with no available stools results from 2 weeks after Dose 2 up to the end of the first efficacy follow-up period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

	HRV $10^{4.7}$ N'= 411		**HRV $10^{5.2}$ N'= 385**		**HRV $10^{5.8}$ N'= 420**		**Placebo N'= 419**	
Category	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
No stools collected	87	21.2	102	26.5	121	28.8	91	21.7
Stools collected but no results available	8	1.9	7	1.8	4	1.0	4	1.0
No stool results available	95	23.1	109	28.3	125	29.8	95	22.7

Notes: N' = number of gastroenteritis episodes reported
n/% = number/percentage of gastroenteritis episodes reported with the specified category

Supplement 4: Summary of demographic characteristics (age calculated in weeks) (total vaccinated cohort for subset planned to receive two doses of study vaccine)

	Parameters or	HRV_4.7 N= 538		HRV_5.2 N= 540		HRV_5.8 N= 540		Placebo N= 537		Total N= 2155	
Characteristics	**Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at first dose (Weeks)	Mean	8.3	-	8.4	-	8.3	-	8.4	-	8.3	-
	SD	1.52	-	1.50	-	1.51	-	1.58	-	1.50	-
	Median	8	-	8	-	8	-	8	-	8	-
	Minimum	6	-	6	-	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	240	44.6	265	49.1	254	47.0	267	49.7	1026	47.6
	Male	298	55.4	275	50.9	286	53.0	270	50.3	1129	52.4
Race	Black	21	3.9	17	3.1	19	3.5	13	2.4	70	3.2
	White/Caucasian	114	21.2	132	24.4	140	25.9	134	25.0	520	24.1
	Oriental	0	0.0	0	0.0	0	0.0	1	0.2	1	0.0
	Other	403	74.9	391	72.4	381	70.6	389	72.4	1564	72.6
Height(cm)	Mean	57.3	-	57.4	-	57.4	-	57.6	-	57.4	-
	SD	2.78	-	2.66	-	2.90	-	2.92	-	2.80	-
	Median	57	-	57	-	57	-	57	-	57	-
	Unknown	2	-	2	-	1	-	1	-	6	-
Weight(kg)	Mean	5.3	-	5.3	-	5.3	-	5.3	-	5.3	-
	SD	0.75	-	0.69	-	0.76	-	0.76	-	0.70	-
	Median	5.2	-	5.3	-	5.3	-	5.3	-	5.3	-
	Unknown	2	-	0	-	1	-	1	-	4	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

Supplement 5: Summary of demographic characteristics (age calculated in weeks) in Brazil (total vaccinated cohort for subset planned to receive two doses of study vaccine)

	Parameters or	HRV_4.7 N= 194		HRV_5.2 N= 196		HRV_5.8 N= 194		Placebo N= 194		Total N= 778	
Characteristics	**Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at first dose (Weeks)	Mean	8.3	-	8.3	-	8.2	-	8.6	-	8.3	-
	SD	1.85	-	1.84	-	1.74	-	1.98	-	1.90	-
	Median	8	-	8	-	8	-	9	-	8	-
	Minimum	6	-	6	-	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	82	42.3	94	48.0	93	47.9	98	50.5	367	47.2
	Male	112	57.7	102	52.0	101	52.1	96	49.5	411	52.8
Race	Black	14	7.2	10	5.1	11	5.7	8	4.1	43	5.5
	White/Caucasian	21	10.8	35	17.9	24	12.4	36	18.6	116	14.9
	Other	159	82.0	151	77.0	159	82.0	150	77.3	619	79.6
Height(cm)	Mean	56.8	-	57.1	-	56.7	-	57.1	-	56.9	-
	SD	2.51	-	2.51	-	2.90	-	2.85	-	2.70	-
	Median	57	-	57	-	57	-	57	-	57	-
	Unknown	2	-	2	-	1	-	1	-	6	-
Weight(kg)	Mean	5.4	-	5.4	-	5.2	-	5.4	-	5.3	-
	SD	0.83	-	0.77	-	0.74	-	0.79	-	0.80	-
	Median	5.2	-	5.35	-	5.2	-	5.3	-	5.2	-
	Unknown	2	-	0	-	1	-	1	-	4	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

Supplement 6: Summary of demographic characteristics (age calculated in weeks) in Mexico (total vaccinated cohort for subset planned to receive two doses of study vaccine)

	Parameters or	HRV_4.7 N= 101		HRV_5.2 N= 101		HRV_5.8 N= 102		Placebo N= 101		Total N= 405	
Characteristics	**Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at first dose (Weeks)	Mean	7.6	-	7.9	-	7.6	-	7.8	-	7.7	-
	SD	1.37	-	1.49	-	1.59	-	1.51	-	1.50	-
	Median	8	-	8	-	7	-	8	-	8	-
	Minimum	6	-	6	-	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	34	33.7	52	51.5	47	46.1	44	43.6	177	43.7
	Male	67	66.3	49	48.5	55	53.9	57	56.4	228	56.3
Race	Black	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White/Caucasian	6	5.9	5	5.0	5	4.9	2	2.0	18	4.4
	Other	95	94.1	96	95.0	97	95.1	99	98.0	387	95.6
Height(cm)	Mean	55.2	-	55.4	-	55.3	-	55.7	-	55.4	-
	SD	2.23	-	2.07	-	2.39	-	2.42	-	2.30	-
	Median	55	-	55	-	55	-	56	-	55	-
Weight(kg)	Mean	4.9	-	5.0	-	4.9	-	5.0	-	4.9	-
	SD	0.61	-	0.60	-	0.76	-	0.62	-	0.70	-
	Median	5	-	5.1	-	4.8	-	5	-	5	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

Supplement 7: Summary of demographic characteristics (age calculated in weeks) in Venezuela (total vaccinated cohort for subset planned to receive two doses of study vaccine)

	Parameters or	HRV_4.7 N= 243		HRV_5.2 N= 243		HRV_5.8 N= 244		Placebo N= 242		Total N= 972	
Characteristics	**Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at first dose (Weeks)	Mean	8.6	-	8.6	-	8.6	-	8.6	-	8.6	-
	SD	1.16	-	1.12	-	1.14	-	1.11	-	1.10	-
	Median	8	-	8	-	8	-	8	-	8	-
	Minimum	6	-	7	-	7	-	7	-	6	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	124	51.0	119	49.0	114	46.7	125	51.7	482	49.6
	Male	119	49.0	124	51.0	130	53.3	117	48.3	490	50.4
Race	Black	7	2.9	7	2.9	8	3.3	5	2.1	27	2.8
	White/Caucasian	87	35.8	92	37.9	111	45.5	96	39.7	386	39.7
	Oriental	0	0.0	0	0.0	0	0.0	1	0.4	1	0.1
	Other	149	61.3	144	59.3	125	51.2	140	57.9	558	57.4
Height(cm)	Mean	58.5	-	58.5	-	58.8	-	58.8	-	58.6	-
	SD	2.59	-	2.45	-	2.31	-	2.62	-	2.50	-
	Median	59	-	59	-	59	-	59	-	59	-
Weight(kg)	Mean	5.4	-	5.4	-	5.5	-	5.5	-	5.5	-
	SD	0.68	-	0.61	-	0.69	-	0.73	-	0.70	-
	Median	5.4	-	5.4	-	5.5	-	5.5	-	5.4	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

Supplement 8: Increase in height and weight from Visit 1 to Visit 2, 3 and 4 (total vaccinated cohort for subset planned to receive two doses of study vaccine)

Visit	Characteristics	Parameters	HRV_4.7 N = (538)	HRV_5.2 N = (540)	HRV_5.8 N = (540)	Placebo N = (537)	Total N = (2155)
			Value	Value	Value	Value	Value
Visit 2	Increase in height (cm) from Visit 1	Mean	5.8	5.8	5.9	5.7	5.8
		SD	2.42	2.22	2.42	2.58	2.41
		Median	6	6	6	6	6
		Unknown	29	28	27	15	99
	Increase in weight (kg) from Visit 1	Mean	1.6	1.6	1.6	1.5	1.6
		SD	0.55	0.55	0.52	0.54	0.54
		Median	1.5	1.5	1.5	1.5	1.5
		Unknown	29	27	26	15	97
Visit 3	Increase in height (cm) from Visit 1	Mean	9.7	9.3	9.7	9.5	9.6
		SD	2.48	3.87	2.65	2.71	2.98
		Median	10	9	10	9	10
		Unknown	35	36	37	27	135
	Increase in weight (kg) from Visit 1	Mean	2.5	2.5	2.5	2.4	2.5
		SD	0.75	0.68	0.74	0.71	0.72
		Median	2.4	2.4	2.4	2.4	2.4
		Unknown	35	35	37	27	134
Visit 4	Increase in height (cm) from Visit 1	Mean	17.3	17.1	17.1	17	17.1
		SD	2.83	2.74	2.69	2.81	2.77
		Median	17	17	17	17	17
		Unknown	43	43	44	33	163
	Increase in weight (kg) from Visit 1	Mean	4.0	4.0	4.0	4.0	4.0
		SD	0.97	0.87	0.98	0.9	0.93
		Median	4	3.9	3.9	3.9	3.9
		Unknown	41	42	42	37	162

Notes: N = Total number of subjects by group or in total (sum of all groups)
Value = value of the considered parameter
SD = standard deviation

Supplement 9: Summary of demographic characteristics (age calculated in weeks) (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

	Parameters or	HRV_4.7 N= 395		HRV_5.2 N= 377		HRV_5.8 N= 381		Placebo N= 373		Total N= 1526	
Characteristics	**Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age at first dose (Weeks)	Mean	8.2	-	8.4	-	8.3	-	8.3	-	8.3	-
	SD	1.49	-	1.44	-	1.45	-	1.48	-	1.50	-
	Median	8	-	8	-	8	-	8	-	8	-
	Minimum	6	-	6	-	6	-	6	-	6	-
	Maximum	12	-	12	-	12	-	12	-	12	-
Gender	Female	182	46.1	195	51.7	180	47.2	186	49.9	743	48.7
	Male	213	53.9	182	48.3	201	52.8	187	50.1	783	51.3
Race	Black	18	4.6	10	2.7	13	3.4	10	2.7	51	3.3
	White/Caucasian	80	20.3	96	25.5	104	27.3	95	25.5	375	24.6
	Other	297	75.2	271	71.9	264	69.3	268	71.8	1100	72.1
Height(cm)	Mean	57.2	-	57.4	-	57.6	-	57.6	-	57.5	-
	SD	2.79	-	2.53	-	2.87	-	2.83	-	2.80	-
	Median	57	-	57	-	58	-	58	-	57	-
	Unknown	1	-	1	-	0	-	1	-	3	-
Weight(kg)	Mean	5.3	-	5.3	-	5.3	-	5.3	-	5.3	-
	SD	0.74	-	0.65	-	0.73	-	0.75	-	0.70	-
	Median	5.2	-	5.3	-	5.3	-	5.3	-	5.3	-
	Unknown	2	-	0	-	1	-	0	-	3	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

Supplement 10: Percentage of subjects who received OPV at birth (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

HRV_4.7			HRV_5.2			HRV_5.8			Placebo		
N	n	%	N	n	%	N	n	%	N	n	%
395	54	13.7	377	61	16.2	381	45	11.8	373	59	15.8

Notes: N = Number of subjects in the considered cohort
n/% = number/percentage of subjects with OPV given at birth

Supplement 11: Summary of feeding criteria (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Dose	Group	N	Feeding criteria					
			Breast milk		Infant formula		Both	
			n	%	n	%	n	%
1	HRV_4.7	395	218	55.2	14	3.5	163	41.3
	HRV_5.2	377	192	50.9	15	4.0	170	45.1
	HRV_5.8	381	212	55.6	16	4.2	153	40.2
	Placebo	373	214	57.4	14	3.8	145	38.9
2	HRV_4.7	388	176	45.4	32	8.2	180	46.4
	HRV_5.2	369	171	46.3	36	9.8	162	43.9
	HRV_5.8	371	160	43.1	42	11.3	169	45.6
	Placebo	372	182	48.9	37	9.9	153	41.1

Notes: N = number of subjects having received the considered dose and with available data
n/% = number/percentage of subjects with the specified feeding criteria

Supplement 12: Duration (in years) of the follow-up period from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Duration (years) Of follow-up period	HRV $10^{4.7}$ N= 468	HRV $10^{5.2}$ N= 460	HRV $10^{5.8}$ N= 464	Placebo N= 454
Total	282.6	276.5	277.8	271.9
Mean	0.604	0.601	0.599	0.599
Minimum	0.115	0.027	0.003	0.016
Q1	0.567	0.566	0.567	0.564
Median	0.595	0.597	0.597	0.595
Q3	0.649	0.640	0.641	0.638
Maximum	1.025	0.841	1.027	0.767

Notes: N = number of subjects included in each group
Total = sum of follow-up period expressed in year
Q1 = 25th percentile
Q3 = 75th percentile

Supplement 13: Percentage of subjects who reported GE episode(s) from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Event	Total number of episode reported	HRV $10^{4.7}$ N= 468		HRV $10^{5.2}$ N= 460		HRV $10^{5.8}$ N= 464		Placebo N= 454	
		n	%	n	%	n	%	n	%
GE	**1**	87	18.6	84	18.3	83	17.9	109	24.0
	2	54	11.5	45	9.8	55	11.9	44	9.7
	3	27	5.8	26	5.7	31	6.7	37	8.1
	4	15	3.2	12	2.6	10	2.2	14	3.1
	5	11	2.4	5	1.1	9	1.9	6	1.3
	6	2	0.4	4	0.9	1	0.2	3	0.7
	7	0	0.0	4	0.9	5	1.1	1	0.2
	8	1	0.2	1	0.2	1	0.2	0	0.0
	Any	197	42.1	181	39.3	195	42.0	214	47.1
RV GE	**1**	21	4.5	22	4.8	15	3.2	47	10.4
	2	0	0.0	0	0.0	0	0.0	2	0.4
	Any	21	4.5	22	4.8	15	3.2	49	10.8

Notes:
N = number of subjects included in each group
n/% = number/percentage of subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified symptom

Supplement 14: Characteristics of GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 411		HRV $10^{5.2}$ N'= 385		HRV $10^{5.8}$ N'= 420		Placebo N'= 419	
		Value or n	Value or n	Value or n	Value or n	Value or n	Value or n	Value or n	Value or n
Severity Score	**Mean**	7.64	-	7.01	-	7.00	-	8.03	-
	SD	4.05	-	3.84	-	3.75	-	4.24	-
	Median	7.00	-	6.00	-	6.00	-	7.00	-
	Minimum	2.00	-	2.00	-	2.00	-	2.00	-
	Maximum	20.00	-	20.00	-	20.00	-	20.00	-
Duration of looser than Normal stools (days)	**1-4 days**	253	61.6	246	63.9	265	63.1	255	60.9
	5 days	30	7.3	32	8.3	36	8.6	32	7.6
	≥ 6 days	128	31.1	107	27.8	119	28.3	132	31.5
Maximum number of looser Than normal stools/24 hours	**1-3**	67	16.3	73	19.0	86	20.5	72	17.2
	4-5	184	44.8	181	47.0	192	45.7	176	42.0
	≥ 6	160	38.9	131	34.0	142	33.8	171	40.8
Duration of vomiting	**0 day**	238	57.9	234	60.8	260	61.9	225	53.7
	1 day	77	18.7	77	20.0	83	19.8	89	21.2
	2 days	36	8.8	33	8.6	40	9.5	43	10.3
	≥ 3 days	60	14.6	41	10.6	37	8.8	62	14.8
Maximum number of Episodes of Vomiting/24 hours	**0**	238	57.9	234	60.8	260	61.9	225	53.7
	1	47	11.4	37	9.6	60	14.3	40	9.5
	2	90	21.9	93	24.2	78	18.6	107	25.5
	≥ 3	36	8.8	21	5.5	22	5.2	47	11.2
Maximum fever reported /24 hours (measured rectally)	**< 37.1°C**	178	43.3	220	57.1	217	51.7	199	47.5
	37.1-38.4°C	128	31.1	91	23.6	103	24.5	108	25.8
	38.5-38.9°C	36	8.8	27	7.0	37	8.8	34	8.1
	≥ 39°C	69	16.8	47	12.2	63	15.0	78	18.6
Treatment	**none**	127	30.9	131	34.0	144	34.3	109	26.0
	Rehydration	263	64.0	239	62.1	259	61.7	282	67.3
	Hospitalisation	21	5.1	15	3.9	17	4.0	28	6.7
Dehydration	**none**	342	83.2	323	83.9	359	85.5	326	77.8
	1-5%	56	13.6	52	13.5	48	11.4	72	17.2
	≥ 6%	13	3.2	10	2.6	13	3.1	21	5.0

Notes: N' = number of GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 15: Characteristics of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 21		HRV $10^{5.2}$ N'= 22		HRV $10^{5.8}$ N'= 15		Placebo N'= 51	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	**Mean**	11.05	-	8.82	-	9.27	-	12.35	-
	SD	4.36	-	4.37	-	3.47	-	4.40	-
	Median	11.00	-	8.00	-	9.00	-	13.00	-
	Minimum	3.00	-	2.00	-	3.00	-	2.00	-
	Maximum	18.00	-	16.00	-	16.00	-	20.00	-
Duration of looser than Normal stools (days)	**1-4 days**	14	66.7	13	59.1	10	66.7	26	51.0
	5 days	5	23.8	4	18.2	0	0.0	12	23.5
	≥ 6 days	2	9.5	5	22.7	5	33.3	13	25.5
Maximum number of looser than normal stools /24 hours	**1-3**	1	4.8	3	13.6	2	13.3	7	13.7
	4-5	7	33.3	9	40.9	7	46.7	10	19.6
	≥ 6	13	61.9	10	45.5	6	40.0	34	66.7
Duration of vomiting	**0 day**	4	19.0	9	40.9	7	46.7	6	11.8
	1 day	8	38.1	4	18.2	3	20.0	14	27.5
	2 days	2	9.5	4	18.2	3	20.0	10	19.6
	≥ 3 days	7	33.3	5	22.7	2	13.3	21	41.2
Maximum number of Episodes of Vomiting/24 hours	**0**	4	19.0	9	40.9	7	46.7	6	11.8
	1	3	14.3	1	4.5	0	0.0	5	9.8
	2	9	42.9	11	50.0	8	53.3	21	41.2
	≥ 3	5	23.8	1	4.5	0	0.0	19	37.3
Maximum fever reported /24 hours (measured rectally)	**< 37.1°C**	4	19.0	15	68.2	3	20.0	7	13.7
	37.1-38.4°C	5	23.8	1	4.5	5	33.3	14	27.5
	38.5-38.9°C	7	33.3	2	9.1	2	13.3	11	21.6
	≥ 39°C	5	23.8	4	18.2	5	33.3	19	37.3
Treatment	**none**	3	14.3	3	13.6	3	20.0	4	7.8
	Rehydration	13	61.9	18	81.8	9	60.0	33	64.7
	Hospitalisation	5	23.8	1	4.5	3	20.0	14	27.5
Dehydration	**none**	11	52.4	14	63.6	11	73.3	27	52.9
	1-5%	8	38.1	7	31.8	2	13.3	15	29.4
	≥ 6%	2	9.5	1	4.5	2	13.3	9	17.6

Notes: N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 16: Characteristics of RV GE episodes of G1 wild type, reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 12		HRV $10^{5.2}$ N'= 6		HRV $10^{5.8}$ N'= 7		Placebo N'= 30	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	**Mean**	10.08	-	10.50	-	9.00	-	10.80	-
	SD	4.19	-	2.88	-	2.77	-	3.98	-
	Median	11.00	-	11.50	-	10.00	-	11.00	-
	Minimum	3.00	-	7.00	-	3.00	-	2.00	-
	Maximum	15.00	-	14.00	-	11.00	-	18.00	-
Duration of looser than Normal stools (days)	**1-4 days**	10	83.3	6	100.0	5	71.4	19	63.3
	5 days	2	16.7	0	0.0	0	0.0	7	23.3
	≥ 6 days	0	0.0	0	0.0	2	28.6	4	13.3
Maximum number of looser than normal stools /24 hours	**1-3**	1	8.3	0	0.0	1	14.3	5	16.7
	4-5	4	33.3	2	33.3	2	28.6	7	23.3
	≥ 6	7	58.3	4	66.7	4	57.1	18	60.0
Duration of vomiting	**0 day**	3	25.0	1	16.7	4	57.1	5	16.7
	1 day	5	41.7	1	16.7	2	28.6	9	30.0
	2 days	1	8.3	1	16.7	1	14.3	6	20.0
	≥ 3 days	3	25.0	3	50.0	0	0.0	10	33.3
Maximum number of episodes of vomiting/24 hours	**0**	3	25.0	1	16.7	4	57.1	5	16.7
	1	2	16.7	0	0.0	0	0.0	5	16.7
	2	5	41.7	4	66.7	3	42.9	9	30.0
	≥ 3	2	16.7	1	16.7	0	0.0	11	36.7
Maximum fever reported /24 hours (measured rectally)	**< 37.1°C**	2	16.7	3	50.0	1	14.3	5	16.7
	37.1-38.4°C	3	25.0	0	0.0	1	14.3	8	26.7
	38.5-38.9°C	4	33.3	2	33.3	1	14.3	6	20.0
	≥ 39°C	3	25.0	1	16.7	4	57.1	11	36.7
Treatment	**none**	2	16.7	1	16.7	1	14.3	4	13.3
	Rehydration	8	66.7	5	83.3	5	71.4	24	80.0
	Hospitalisation	2	16.7	0	0.0	1	14.3	2	6.7
Dehydration	**none**	7	58.3	3	50.0	6	85.7	21	70.0
	1-5%	4	33.3	3	50.0	0	0.0	9	30.0
	≥ 6%	1	8.3	0	0.0	1	14.3	0	0.0

Notes: N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 17: Characteristics of RV GE episodes of G9 type, reported from 2 weeks after Dose 2 up to the end of the first efficacy period (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 8		HRV $10^{5.2}$ N'= 14		HRV $10^{5.8}$ N'= 6		Placebo N'= 15	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	**Mean**	11.63	-	8.79	-	10.17	-	14.87	-
	SD	4.24	-	4.76	-	4.71	-	4.00	-
	Median	11.50	-	8.00	-	9.50	-	16.00	-
	Minimum	6.00	-	2.00	-	4.00	-	6.00	-
	Maximum	17.00	-	16.00	-	16.00	-	20.00	-
Duration of looser than Normal stools (days)	**1-4 days**	3	37.5	5	35.7	4	66.7	3	20.0
	5 days	3	37.5	4	28.6	0	0.0	5	33.3
	≥ 6 days	2	25.0	5	35.7	2	33.3	7	46.7
Maximum number of looser than normal stools /24 hours	**1-3**	0	0.0	2	14.3	1	16.7	1	6.7
	4-5	3	37.5	7	50.0	3	50.0	2	13.3
	≥ 6	5	62.5	5	35.7	2	33.3	12	80.0
Duration of vomiting	**0 day**	1	12.5	6	42.9	2	33.3	1	6.7
	1 day	3	37.5	3	21.4	1	16.7	3	20.0
	2 days	1	12.5	3	21.4	1	16.7	3	20.0
	≥ 3 days	3	37.5	2	14.3	2	33.3	8	53.3
Maximum number of Episodes of Vomiting/24 hours	**0**	1	12.5	6	42.9	2	33.3	1	6.7
	1	1	12.5	1	7.1	0	0.0	0	0.0
	2	4	50.0	7	50.0	4	66.7	8	53.3
	≥ 3	2	25.0	0	0.0	0	0.0	6	40.0
Maximum fever reported /24 hours (measured rectally)	**< 37.1°C**	2	25.0	10	71.4	2	33.3	2	13.3
	37.1-38.4°C	2	25.0	1	7.1	2	33.3	5	33.3
	38.5-38.9°C	3	37.5	0	0.0	1	16.7	4	26.7
	≥ 39°C	1	12.5	3	21.4	1	16.7	4	26.7
Treatment	**none**	1	12.5	2	14.3	1	16.7	0	0.0
	Rehydration	5	62.5	11	78.6	3	50.0	5	33.3
	Hospitalisation	2	25.0	1	7.1	2	33.3	10	66.7
Dehydration	**none**	4	50.0	9	64.3	3	50.0	3	20.0
	1-5%	4	50.0	4	28.6	2	33.3	5	33.3
	≥ 6%	0	0.0	1	7.1	1	16.7	7	46.7

Notes: N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 18: Percentage of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period, by mixed infection (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

	HRV $10^{4.7}$ N'= 21		HRV $10^{5.2}$ N'= 22		HRV $10^{5.8}$ N'= 15		Placebo N'= 51	
Mixed infection	**n**	**%**	**n**	**%**	**n**	**%**	**N**	**%**
At least one mixed infection	1	4.8	0	0.0	2	13.3	3	5.9
Campylobacter	0	0.0	0	0.0	0	0.0	0	0.0
Salmonella	1	4.8	0	0.0	0	0.0	0	0.0
Shigella	0	0.0	0	0.0	1	6.7	1	2.0
Ag-E.Coli	0	0.0	0	0.0	0	0.0	0	0.0
ETEC	0	0.0	0	0.0	0	0.0	0	0.0
EPEC	0	0.0	0	0.0	0	0.0	1	2.0
EAgEC	0	0.0	0	0.0	1	6.7	1	2.0
EIEC	0	0.0	0	0.0	0	0.0	0	0.0

Notes: N'= number of RV GE episodes reported
n/% = number/percentage of mixed RV GE episodes reported in each group, among all RV GE episodes reported in the first efficacy follow-up period

Supplement 19: Percentage of vaccinees reporting RV GE episodes from 2 weeks after Dose 2 up to the end of the first efficacy period, by status of anti-rotavirus IgA antibody concentration at two months after Dose 2 (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Anti-rotavirus	**HRV $10^{4.7}$**					**HRV $10^{5.2}$**				
Antibody status				**95%CI**					**95%CI**	
At Visit 3	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Negative	64	7	10.9	4.5	21.3	52	6	11.5	4.4	23.4
Positive	103	1	1.0	0.0	5.3	100	2	2.0	0.2	7.0
Unknown	301	13	4.3	2.3	7.3	308	14	4.5	2.5	7.5

Anti-rotavirus	**HRV $10^{5.8}$**					**Pooled HRV groups**				
Antibody status				**95%CI**					**95%CI**	
At Visit 3	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Negative	53	6	11.3	4.3	23.0	169	19	11.2	6.9	17.0
Positive	106	2	1.9	0.2	6.7	309	5	1.6	0.5	3.7
Unknown	305	7	2.3	0.9	4.7	914	34	3.7	2.6	5.2

Notes: N = number of subjects included in the vaccine group with the specified status for anti-rotavirus IgA antibody concentration two months after Dose 2
n/% = number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration two months after Dose 2 reporting at least one RV GE episode from 2 weeks after Dose 2 up to the end of the first efficacy period
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 20: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

Group	N	n	T (year)	n/T value	95%CI LL	95%CI UL	n/N %	95%CI LL	95%CI UL	Vaccine Efficacy %	95%CI LL	95%CI UL	p-value
G1 wild type													
HRV $10^{4.7}$	468	12	279.1	0.043	0.024	0.076	2.6	1.3	4.4	59.9	18.9	81.3	0.006
HRV $10^{5.2}$	460	6	274.7	0.022	0.010	0.049	1.3	0.5	2.8	79.6	49.9	93.1	<0.001
HRV $10^{5.8}$	464	7	275.3	0.025	0.012	0.053	1.5	0.6	3.1	76.4	44.9	91.3	<0.001
Pooled HRV Groups	1392	25	829.1	0.030	0.020	0.045	1.8	1.2	2.6	71.9	50.3	84.2	<0.001
Placebo	454	29	263.0	0.110	0.077	0.159	6.4	4.3	9.0	-	-	-	-
G9													
HRV $10^{4.7}$	468	8	279.9	0.029	0.014	0.057	1.7	0.7	3.3	48.3	-30.0	81.0	0.141
HRV $10^{5.2}$	460	14	271.0	0.052	0.031	0.087	3.0	1.7	5.1	7.9	-105	58.8	0.852
HRV $10^{5.8}$	464	7	275.4	0.025	0.012	0.053	1.5	0.6	3.1	54.3	-19.0	84.3	0.086
Pooled HRV Groups	1392	29	826.2	0.035	0.024	0.051	2.1	1.4	3.0	36.9	-26.5	67.3	0.156
Placebo	454	15	266.5	0.056	0.034	0.093	3.3	1.9	5.4	-	-	-	-
Pooled Non G1 (G2, G3, G4, G9)													
HRV $10^{4.7}$	468	9	279.8	0.032	0.017	0.062	1.9	0.9	3.6	56.3	-0.3	82.5	0.037
HRV $10^{5.2}$	460	14	271.0	0.052	0.031	0.087	3.0	1.7	5.1	30.9	-43.8	67.7	0.299
HRV $10^{5.8}$	464	8	274.7	0.029	0.015	0.058	1.7	0.7	3.4	60.9	7.2	85.1	0.021
Pooled HRV Groups	1392	31	825.5	0.038	0.026	0.053	2.2	1.5	3.1	49.4	6.4	72.1	0.020
Placebo	454	20	265.6	0.075	0.049	0.117	4.4	2.7	6.7	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T= sum of follow-up period expressed in year censored at the first occurrence of RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one RV GE episode in each group
n/T= person-year rate of RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 21: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
G1 wild type													
HRV $10^{4.7}$	468	7	280.7	0.025	0.012	0.052	1.5	0.6	3.1	57.6	-9.0	85.2	0.057
HRV $10^{5.2}$	460	4	275.4	0.015	0.005	0.039	0.9	0.2	2.2	75.3	23.5	94.0	0.006
HRV $10^{5.8}$	464	2	276.9	0.007	0.002	0.029	0.4	0.1	1.5	87.8	48.0	98.6	<0.001
Pooled HRV Groups	1392	13	833.0	0.016	0.009	0.027	0.9	0.5	1.6	73.5	41.2	88.3	<0.001
Placebo	454	16	267.2	0.060	0.037	0.098	3.5	2.0	5.7	-	-	-	-
G9													
HRV $10^{4.7}$	468	4	281.6	0.014	0.005	0.038	0.9	0.2	2.2	70.2	3.4	92.9	0.027
HRV $10^{5.2}$	460	6	274.3	0.022	0.010	0.049	1.3	0.5	2.8	54.4	-28.5	85.8	0.109
HRV $10^{5.8}$	464	3	277.0	0.011	0.003	0.034	0.6	0.1	1.9	77.4	17.8	95.9	0.011
Pooled HRV Groups	1392	13	832.8	0.016	0.009	0.027	0.9	0.5	1.6	67.4	23.6	86.1	0.005
Placebo	454	13	267.6	0.049	0.028	0.084	2.9	1.5	4.8	-	-	-	-
Pooled Non G1 (G2, G3, G4, G9)													
HRV $10^{4.7}$	468	5	281.5	0.018	0.007	0.043	1.1	0.3	2.5	71.5	19.4	91.8	0.009
HRV $10^{5.2}$	460	6	274.3	0.022	0.010	0.049	1.3	0.5	2.8	65.2	7.4	88.8	0.020
HRV $10^{5.8}$	464	3	277.0	0.011	0.003	0.034	0.6	0.1	1.9	82.7	40.3	96.8	0.001
Pooled HRV Groups	1392	14	832.8	0.017	0.010	0.028	1.0	0.6	1.7	73.1	42.1	87.7	<0.001
Placebo	454	17	266.7	0.064	0.040	0.103	3.7	2.2	5.9	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T= sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 22: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
Brazil													
HRV $10^{4.7}$	163	16	101.7	0.157	0.096	0.257	9.8	5.7	15.5	39.1	-19.6	69.7	0.127
HRV $10^{5.2}$	153	18	93.5	0.193	0.121	0.306	11.8	7.1	18.0	27.0	-40.4	62.7	0.320
HRV $10^{5.8}$	170	10	107.1	0.093	0.050	0.173	5.9	2.9	10.6	63.5	20.8	84.4	0.004
Pooled HRV Groups	486	44	302.3	0.146	0.108	0.196	9.1	6.7	12.0	43.8	3.4	66.6	0.022
Placebo	149	24	89.8	0.267	0.179	0.399	16.1	10.6	23.0	-	-	-	-
Mexico													
HRV $10^{4.7}$	79	1	46.5	0.022	0.003	0.153	1.3	0.0	6.9	90.8	38.0	99.8	0.003
HRV $10^{5.2}$	86	3	48.8	0.061	0.020	0.191	3.5	0.7	9.9	74.7	6.3	95.4	0.028
HRV $10^{5.8}$	78	3	43.7	0.069	0.022	0.213	3.8	0.8	10.8	72.1	-3.3	95.0	0.031
Pooled HRV Groups	243	7	139.0	0.050	0.024	0.106	2.9	1.2	5.8	79.1	42.5	93.0	<0.001
Placebo	87	12	46.4	0.259	0.147	0.456	13.8	7.3	22.9	-	-	-	-
Venezuela													
HRV $10^{4.7}$	226	4	128.3	0.031	0.012	0.083	1.8	0.5	4.5	70.3	3.9	93.0	0.026
HRV $10^{5.2}$	221	1	126.1	0.008	0.001	0.056	0.5	0.0	2.5	92.4	49.5	99.8	<0.001
HRV $10^{5.8}$	216	2	121.4	0.016	0.004	0.066	0.9	0.1	3.3	84.5	31.4	98.3	0.006
Pooled HRV Groups	663	7	375.8	0.019	0.009	0.039	1.1	0.4	2.2	82.3	52.3	94.0	<0.001
Placebo	218	13	120.3	0.108	0.063	0.186	6.0	3.2	10.0	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one RV GE episode in each group
n/T = person-year rate of RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 23: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (ATP cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
Brazil													
HRV $10^{4.7}$	163	9	104.3	0.086	0.045	0.166	5.5	2.6	10.2	56.7	-0.4	82.7	0.030
HRV $10^{5.2}$	153	9	97.2	0.093	0.048	0.178	5.9	2.7	10.9	53.9	-7.0	81.6	0.047
HRV $10^{5.8}$	170	4	109.1	0.037	0.014	0.098	2.4	0.6	5.9	81.5	44.5	95.4	<0.001
Pooled HRV Groups	486	22	310.6	0.071	0.047	0.108	4.5	2.9	6.8	64.5	30.7	81.7	<0.001
Placebo	149	19	91.2	0.208	0.133	0.327	12.8	7.9	19.2	-	-	-	-
Mexico													
HRV $10^{4.7}$	79	1	46.5	0.022	0.003	0.153	1.3	0.0	6.9	84.3	-22.5	99.7	0.066
HRV $10^{5.2}$	86	0	49.8	0.000	Und.	Und.	0.0	0.0	4.2	100.0	29.8	100.0	0.014
HRV $10^{5.8}$	78	0	45.2	0.000	Und.	Und.	0.0	0.0	4.6	100.0	22.6	100.0	0.015
Pooled HRV Groups	243	1	141.5	0.007	0.001	0.050	0.4	0.0	2.3	94.9	60.2	99.9	<0.001
Placebo	87	7	48.4	0.145	0.069	0.304	8.0	3.3	15.9	-	-	-	-
Venezuela													
HRV $10^{4.7}$	226	2	128.9	0.016	0.004	0.062	0.9	0.1	3.2	75.9	-20.8	97.5	0.058
HRV $10^{5.2}$	221	1	126.1	0.008	0.001	0.056	0.5	0.0	2.5	87.7	8.0	99.7	0.020
HRV $10^{5.8}$	216	1	121.7	0.008	0.001	0.058	0.5	0.0	2.6	87.4	5.9	99.7	0.037
Pooled HRV Groups	663	4	376.8	0.011	0.004	0.028	0.6	0.2	1.5	83.6	38.6	96.4	0.002
Placebo	218	8	122.2	0.065	0.033	0.131	3.7	1.6	7.1	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
und = cannot be estimate
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 24: Duration (in years) of the follow-up period from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Duration (years) of follow-up period	**HRV $10^{4.7}$ N= 507**	**HRV $10^{5.2}$ N= 508**	**HRV $10^{5.8}$ N= 512**	**Placebo N= 517**
Total	306.8	305.9	307.3	310.6
Mean	0.605	0.602	0.600	0.601
Minimum	0.115	0.027	0.003	0.016
Q1	0.567	0.567	0.567	0.567
Median	0.600	0.597	0.599	0.597
Q3	0.652	0.641	0.641	0.638
Maximum	1.025	0.841	1.027	1.030

Notes: N = number of subjects included in each group
Total = sum of follow-up period expressed in year
Q1 = 25th percentile
Q3 = 75th percentile

Supplement 25: Percentage of subjects who reported GE episode(s) from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Event	Total number of episode reported	HRV $10^{4.7}$ N= 507		HRV $10^{5.2}$ N= 508		HRV $10^{5.8}$ N= 512		Placebo N= 517	
		n	%	n	%	n	%	n	%
GE	**1**	96	18.9	96	18.9	95	18.6	124	24.0
	2	58	11.4	53	10.4	60	11.7	53	10.3
	3	32	6.3	33	6.5	37	7.2	43	8.3
	4	19	3.7	14	2.8	13	2.5	16	3.1
	5	11	2.2	5	1.0	11	2.1	12	2.3
	6	2	0.4	4	0.8	2	0.4	3	0.6
	7	0	0.0	5	1.0	6	1.2	1	0.2
	8	2	0.4	1	0.2	1	0.2	1	0.2
	Any	220	43.4	211	41.5	225	43.9	253	48.9
RV GE	**1**	22	4.3	22	4.3	15	2.9	53	10.3
	2	0	0.0	0	0.0	0	0.0	2	0.4
	Any	22	4.3	22	4.3	15	2.9	55	10.6

Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting the specified total number of episode
Any = number and percentage of subjects reporting at least one specified symptom

Supplement 26: Number of GE episodes and RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period, by severity (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Event	Severity	HRV $10^{4.7}$		HRV $10^{5.2}$		HRV $10^{5.8}$		Placebo	
		n	%	n	%	n	%	n	%
Any GE	**Mild (1-6)**	224	48.0	228	50.8	263	53.1	231	44.8
	Moderate (7-10)	141	30.2	136	30.3	149	30.1	153	29.7
	Severe (≥11)	102	21.8	85	18.9	83	16.8	132	25.6
	Any	467	100	449	100	495	100	516	100
RV GE	**Mild (1-6)**	4	18.2	8	36.4	2	13.3	5	8.8
	Moderate (7-10)	5	22.7	4	18.2	8	53.3	12	21.1
	Severe (≥11)	13	59.1	10	45.5	5	33.3	40	70.2
	Any	22	100	22	100	15	100	57	100

Notes: n/%= number/percentage of GE episodes reported in each group, by severity, among all GE episodes reported in the first efficacy follow-up period
Any = any specified symptom, regardless of severity

Supplement 27: Percentage of subjects with RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Serotype	HRV $10^{4.7}$ N= 507		HRV $10^{5.2}$ N= 508		HRV $10^{5.8}$ N= 512		Placebo N= 517	
	n	%	n	%	n	%	n	%
Any	22	4.3	22	4.3	15	2.9	55	10.6
G1 wild type	13	2.6	6	1.2	7	1.4	31	6.0
G2	0	0.0	0	0.0	1	0.2	3	0.6
G3	1	0.2	0	0.0	0	0.0	2	0.4
G4	0	0.0	0	0.0	1	0.2	0	0.0
G9	8	1.6	14	2.8	7	1.4	19	3.7
Canine	0	0.0	0	0.0	0	0.0	1	0.2
Unknown	0	0.0	2	0.4	0	0.0	0	0.0

Notes: N = number of subjects included in each group
n/% = number/percentage of subjects reporting at least once the specified serotype in each group
Any = number of subjects reporting at least one RV GE episode, whatever the serotype

Supplement 28: Characteristics of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 22		HRV $10^{5.2}$ N'= 22		HRV $10^{5.8}$ N'= 15		Placebo N'= 57	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	Mean	11.18	-	8.82	-	9.27	-	12.53	-
	SD	4.31	-	4.37	-	3.47	-	4.27	-
	Median	12.00	-	8.00	-	9.00	-	13.00	-
	Minimum	3.00	-	2.00	-	3.00	-	2.00	-
	Maximum	18.00	-	16.00	-	16.00	-	20.00	-
Duration of looser than Normal stools (days)	1-4 days	14	63.6	13	59.1	10	66.7	28	49.1
	5 days	6	27.3	4	18.2	0	0.0	13	22.8
	≥ 6 days	2	9.1	5	22.7	5	33.3	16	28.1
Maximum number of looser than normal stools/24 hours	1-3	1	4.5	3	13.6	2	13.3	7	12.3
	4-5	8	36.4	9	40.9	7	46.7	12	21.1
	≥ 6	13	59.1	10	45.5	6	40.0	38	66.7
Duration of vomiting	0 day	4	18.2	9	40.9	7	46.7	6	10.5
	1 day	8	36.4	4	18.2	3	20.0	15	26.3
	2 days	2	9.1	4	18.2	3	20.0	11	19.3
	≥ 3 days	8	36.4	5	22.7	2	13.3	25	43.9
Maximum number of episodes of vomiting/24 hours	0	4	18.2	9	40.9	7	46.7	6	10.5
	1	3	13.6	1	4.5	0	0.0	5	8.8
	2	9	40.9	11	50.0	8	53.3	25	43.9
	≥ 3	6	27.3	1	4.5	0	0.0	21	36.8
Maximum fever reported /24 hours (measured rectally)	< 37.1°C	4	18.2	15	68.2	3	20.0	8	14.0
	37.1-38.4°C	5	22.7	1	4.5	5	33.3	16	28.1
	38.5-38.9°C	7	31.8	2	9.1	2	13.3	12	21.1
	≥ 39°C	6	27.3	4	18.2	5	33.3	21	36.8
Treatment	none	3	13.6	3	13.6	3	20.0	4	7.0
	Rehydration	14	63.6	18	81.8	9	60.0	37	64.9
	Hospitalisation	5	22.7	1	4.5	3	20.0	16	28.1
Dehydration	none	12	54.5	14	63.6	11	73.3	29	50.9
	1-5%	8	36.4	7	31.8	2	13.3	19	33.3
	≥ 6%	2	9.1	1	4.5	2	13.3	9	15.8

Notes: N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 29: Characteristics of RV GE episodes of G1 wild type, reported from 2 weeks after Dose 2 stools up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 13		HRV $10^{5.2}$ N'= 6		HRV $10^{5.8}$ N'= 7		Placebo N'= 32	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	Mean	10.38	-	10.50	-	9.00	-	10.88	-
	SD	4.15	-	2.88	-	2.77	-	3.86	-
	Median	11.00	-	11.50	-	10.00	-	11.00	-
	Minimum	3.00	-	7.00	-	3.00	-	2.00	-
	Maximum	15.00	-	14.00	-	11.00	-	18.00	-
Duration of looser than Normal stools (days)	1-4 days	10	76.9	6	100.0	5	71.4	19	59.4
	5 days	3	23.1	0	0.0	0	0.0	8	25.0
	≥ 6 days	0	0.0	0	0.0	2	28.6	5	15.6
Maximum number of looser than normal stools/24 hours	1-3	1	7.7	0	0.0	1	14.3	5	15.6
	4-5	5	38.5	2	33.3	2	28.6	8	25.0
	≥ 6	7	53.8	4	66.7	4	57.1	19	59.4
Duration of vomiting	0 day	3	23.1	1	16.7	4	57.1	5	15.6
	1 day	5	38.5	1	16.7	2	28.6	9	28.1
	2 days	1	7.7	1	16.7	1	14.3	7	21.9
	≥ 3 days	4	30.8	3	50.0	0	0.0	11	34.4
Maximum number of episodes of vomiting/24 hours	0	3	23.1	1	16.7	4	57.1	5	15.6
	1	2	15.4	0	0.0	0	0.0	5	15.6
	2	5	38.5	4	66.7	3	42.9	11	34.4
	≥ 3	3	23.1	1	16.7	0	0.0	11	34.4
Maximum fever reported /24 hours (measured rectally)	< 37.1°C	2	15.4	3	50.0	1	14.3	5	15.6
	37.1-38.4°C	3	23.1	0	0.0	1	14.3	9	28.1
	38.5-38.9°C	4	30.8	2	33.3	1	14.3	7	21.9
	≥ 39°C	4	30.8	1	16.7	4	57.1	11	34.4
Treatment	none	2	15.4	1	16.7	1	14.3	4	12.5
	Rehydration	9	69.2	5	83.3	5	71.4	26	81.3
	Hospitalisation	2	15.4	0	0.0	1	14.3	2	6.3
Dehydration	none	8	61.5	3	50.0	6	85.7	23	71.9
	1-5%	4	30.8	3	50.0	0	0.0	9	28.1
	≥ 6%	1	7.7	0	0.0	1	14.3	0	0.0

Notes: N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 30: Characteristics of RV GE episodes of G9 type, reported from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Characteristics	Parameters or Categories	HRV $10^{4.7}$ N'= 8		HRV $10^{5.2}$ N'= 14		HRV $10^{5.8}$ N'= 6		Placebo N'= 19	
		Value or n	%	Value or n	%	Value or n	%	Value or n	%
Severity Score	Mean	11.63	-	8.79	-	10.17	-	14.89	-
	SD	4.24	-	4.76	-	4.71	-	3.73	-
	Median	11.50	-	8.00	-	9.50	-	15.00	-
	Minimum	6.00	-	2.00	-	4.00	-	6.00	-
	Maximum	17.00	-	16.00	-	16.00	-	20.00	-
Duration of looser than Normal stools (days)	1-4 days	3	37.5	5	35.7	4	66.7	5	26.3
	5 days	3	37.5	4	28.6	0	0.0	5	26.3
	≥ 6 days	2	25.0	5	35.7	2	33.3	9	47.4
Maximum number of looser than normal stools/24 hours	1-3	0	0.0	2	14.3	1	16.7	1	5.3
	4-5	3	37.5	7	50.0	3	50.0	3	15.8
	≥ 6	5	62.5	5	35.7	2	33.3	15	78.9
Duration of vomiting	0 day	1	12.5	6	42.9	2	33.3	1	5.3
	1 day	3	37.5	3	21.4	1	16.7	4	21.1
	2 days	1	12.5	3	21.4	1	16.7	3	15.8
	≥ 3 days	3	37.5	2	14.3	2	33.3	11	57.9
Maximum number of episodes of vomiting/24 hours	0	1	12.5	6	42.9	2	33.3	1	5.3
	1	1	12.5	1	7.1	0	0.0	0	0.0
	2	4	50.0	7	50.0	4	66.7	10	52.6
	≥ 3	2	25.0	0	0.0	0	0.0	8	42.1
Maximum fever reported /24 hours (measured rectally)	< 37.1°C	2	25.0	10	71.4	2	33.3	3	15.8
	37.1-38.4°C	2	25.0	1	7.1	2	33.3	6	31.6
	38.5-38.9°C	3	37.5	0	0.0	1	16.7	4	21.1
	≥ 39°C	1	12.5	3	21.4	1	16.7	6	31.6
Treatment	none	1	12.5	2	14.3	1	16.7	0	0.0
	Rehydration	5	62.5	11	78.6	3	50.0	7	36.8
	Hospitalisation	2	25.0	1	7.1	2	33.3	12	63.2
Dehydration	none	4	50.0	9	64.3	3	50.0	3	15.8
	1-5%	4	50.0	4	28.6	2	33.3	9	47.4
	≥ 6%	0	0.0	1	7.1	1	16.7	7	36.8

Notes: N'= number of RV GE episodes reported in each group
n/% = number/percentage of the specified symptom reported in each group among N'
Value = value of the considered parameter
SD = standard deviation

Supplement 31: Percentage of RV GE episodes reported from 2 weeks after Dose 2 up to the end of the first efficacy period, by mixed infection (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

	HRV $10^{4.7}$ N'= 22		HRV $10^{5.2}$ N'= 22		HRV $10^{5.8}$ N'= 15		Placebo N'= 55	
Mixed infection	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
At least one mixed infection	1	4.5	0	0.0	2	13.3	3	5.5
Campylobacter	0	0.0	0	0.0	0	0.0	0	0.0
Salmonella	1	4.5	0	0.0	0	0.0	0	0.0
Shigella	0	0.0	0	0.0	1	6.7	1	1.8
Ag-E.Coli	0	0.0	0	0.0	0	0.0	0	0.0
ETEC	0	0.0	0	0.0	0	0.0	0	0.0
EPEC	0	0.0	0	0.0	0	0.0	1	1.8
EAgEC	0	0.0	0	0.0	1	6.7	1	1.8
EIEC	0	0.0	0	0.0	0	0.0	0	0.0

Notes: N'= number of RV GE episodes reported
n/% = number/percentage of mixed RV GE episodes reported in each group, among all RV GE episodes reported in the first efficacy follow-up period

Supplement 32: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**p-value**
HRV $10^{4.7}$	507	22	300.2	0.073	0.048	0.111	4.3	2.7	6.5	59.2	32.0	76.3	<0.001
HRV $10^{5.2}$	508	22	297.7	0.074	0.049	0.112	4.3	2.7	6.5	59.3	32.1	76.4	<0.001
HRV $10^{5.8}$	512	15	301.7	0.050	0.030	0.082	2.9	1.6	4.8	72.5	50.6	85.6	<0.001
Pooled HRV Groups	1527	59	899.7	0.066	0.051	0.085	3.9	3.0	5.0	63.7	46.6	75.3	<0.001
Placebo	517	55	292.8	0.188	0.144	0.245	10.6	8.1	13.6	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode in the first efficacy follow-up period, in each group
% = Percentage of subjects reporting at least one RV GE episode in each group
n/T = person-year rate of RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 33: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
Brazil													
HRV $10^{4.7}$	186	16	116.2	0.138	0.084	0.225	8.6	5.0	13.6	41.6	-11.7	70.5	0.077
HRV $10^{5.2}$	182	18	111.9	0.161	0.101	0.255	9.9	6.0	15.2	32.9	-25.7	65.0	0.161
HRV $10^{5.8}$	192	10	121.3	0.082	0.044	0.153	5.2	2.5	9.4	64.7	25.0	84.7	0.002
Pooled HRV Groups	560	44	349.5	0.126	0.094	0.169	7.9	5.8	10.4	46.7	11.1	67.5	0.010
Placebo	190	28	114.0	0.246	0.170	0.356	14.7	10.0	20.6	-	-	-	-
Mexico													
HRV $10^{4.7}$	88	1	52.1	0.019	0.003	0.136	1.1	0.0	6.2	92.1	48.3	99.8	<0.001
HRV $10^{5.2}$	95	3	54.0	0.056	0.018	0.172	3.2	0.7	9.0	78.1	21.6	96.0	0.009
HRV $10^{5.8}$	90	3	50.9	0.059	0.019	0.183	3.3	0.7	9.4	76.9	17.3	95.7	0.010
Pooled HRV Groups	273	7	157.0	0.045	0.021	0.094	2.6	1.0	5.2	82.2	53.0	93.9	<0.001
Placebo	97	14	51.4	0.272	0.161	0.460	14.4	8.1	23.0	-	-	-	-
Venezuela													
HRV $10^{4.7}$	233	5	131.9	0.038	0.016	0.091	2.1	0.7	4.9	62.0	-13.5	89.4	0.057
HRV $10^{5.2}$	231	1	131.8	0.008	0.001	0.054	0.4	0.0	2.4	92.3	49.0	99.8	<0.001
HRV $10^{5.8}$	230	2	129.5	0.015	0.004	0.062	0.9	0.1	3.1	84.6	32.0	98.3	0.007
Pooled HRV Groups	694	8	393.2	0.020	0.010	0.041	1.2	0.5	2.3	79.6	46.9	92.7	<0.001
Placebo	230	13	127.4	0.102	0.059	0.176	5.7	3.0	9.5	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one RV GE episode in each group
n/T = person-year rate of RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 34: Percentage of subjects reporting any RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
G1 wild type													
HRV $10^{4.7}$	507	13	302.9	0.043	0.025	0.074	2.6	1.4	4.3	57.2	15.9	79.5	0.008
HRV $10^{5.2}$	508	6	304.0	0.020	0.009	0.044	1.2	0.4	2.6	80.3	52.1	93.3	<0.001
HRV $10^{5.8}$	512	7	304.8	0.023	0.011	0.048	1.4	0.6	2.8	77.2	47.2	91.5	<0.001
Pooled HRV Groups	1527	26	911.8	0.029	0.019	0.042	1.7	1.1	2.5	71.6	50.6	83.8	<0.001
Placebo	517	31	301.1	0.103	0.072	0.146	6.0	4.1	8.4	-	-	-	-
G9													
HRV $10^{4.7}$	507	8	304.2	0.026	0.013	0.053	1.6	0.7	3.1	57.1	-2.7	83.7	0.049
HRV $10^{5.2}$	508	14	300.3	0.047	0.028	0.079	2.8	1.5	4.6	25.0	-57.7	65.2	0.480
HRV $10^{5.8}$	512	7	304.9	0.023	0.011	0.048	1.4	0.6	2.8	62.8	7.6	86.8	0.027
Pooled HRV Groups	1527	29	909.3	0.032	0.022	0.046	1.9	1.3	2.7	48.3	2.5	72.0	0.028
Placebo	517	19	303.3	0.063	0.040	0.098	3.7	2.2	5.7	-	-	-	-
Pooled Non G1 (G2, G3, G4, G9)													
HRV $10^{4.7}$	507	9	304.1	0.030	0.015	0.057	1.8	0.8	3.3	61.8	14.8	84.4	0.012
HRV $10^{5.2}$	508	14	300.3	0.047	0.028	0.079	2.8	1.5	4.6	40.6	-19.5	71.6	0.136
HRV $10^{5.8}$	512	8	304.2	0.026	0.013	0.053	1.6	0.7	3.1	66.3	22.6	86.9	0.006
Pooled HRV Groups	1527	31	908.6	0.034	0.024	0.049	2.0	1.4	2.9	56.3	22.1	75.2	0.003
Placebo	517	24	302.4	0.079	0.053	0.118	4.6	3.0	6.8	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one RV GE episode in each group
n/T = person-year rate of RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 35: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV $10^{4.7}$	507	13	303.5	0.043	0.025	0.074	2.6	1.4	4.3	66.9	36.7	83.7	<0.001
HRV $10^{5.2}$	508	10	302.5	0.033	0.018	0.061	2.0	0.9	3.6	74.6	48.2	88.7	<0.001
HRV $10^{5.8}$	512	5	305.6	0.016	0.007	0.039	1.0	0.3	2.3	87.4	68.0	96.1	<0.001
Pooled HRV Groups	1527	28	911.5	0.031	0.021	0.044	1.8	1.2	2.6	76.3	60.6	85.9	<0.001
Placebo	517	40	298.0	0.134	0.098	0.183	7.7	5.6	10.4	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 36: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by country (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
Brazil													
HRV $10^{4.7}$	186	9	118.8	0.076	0.039	0.146	4.8	2.2	9.0	60.0	10.3	83.7	0.015
HRV $10^{5.2}$	182	9	115.6	0.078	0.040	0.150	4.9	2.3	9.2	59.1	8.4	83.4	0.016
HRV $10^{5.8}$	192	4	123.3	0.032	0.012	0.086	2.1	0.6	5.2	82.8	49.6	95.7	<0.001
Pooled HRV Groups	560	22	357.8	0.061	0.040	0.093	3.9	2.5	5.9	67.5	39.1	82.8	<0.001
Placebo	190	23	115.4	0.199	0.132	0.300	12.1	7.8	17.6	-	-	-	-
Mexico													
HRV $10^{4.7}$	88	1	52.1	0.019	0.003	0.136	1.1	0.0	6.2	87.8	11.6	99.7	0.020
HRV $10^{5.2}$	95	0	55.0	0.000	Und.	Und.	0.0	0.0	3.8	100.0	48.3	100.0	0.003
HRV $10^{5.8}$	90	0	52.4	0.000	Und.	Und.	0.0	0.0	4.0	100.0	45.4	100.0	0.003
Pooled HRV Groups	273	1	159.5	0.006	0.001	0.045	0.4	0.0	2.0	96.1	71.5	99.9	<0.001
Placebo	97	9	53.4	0.169	0.088	0.324	9.3	4.3	16.9	-	-	-	-
Venezuela													
HRV $10^{4.7}$	233	3	132.5	0.023	0.007	0.070	1.3	0.3	3.7	63.0	-54.2	93.7	0.139
HRV $10^{5.2}$	231	1	131.8	0.008	0.001	0.054	0.4	0.0	2.4	87.6	7.2	99.7	0.020
HRV $10^{5.8}$	230	1	129.9	0.008	0.001	0.055	0.4	0.0	2.4	87.5	6.8	99.7	0.037
Pooled HRV Groups	694	5	394.2	0.013	0.005	0.030	0.7	0.2	1.7	79.3	28.2	94.7	0.005
Placebo	230	8	129.2	0.062	0.031	0.124	3.5	1.5	6.7	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
und = cannot be estimated
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 37: Percentage of subjects reporting severe RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period, by serotype (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	N	n	(year)	value	LL	UL	%	LL	UL	%	LL	UL	p-value
G1 wild type													
HRV $10^{4.7}$	507	8	304.5	0.026	0.013	0.053	1.6	0.7	3.1	54.7	-9.5	82.9	0.072
HRV $10^{5.2}$	508	4	304.7	0.013	0.005	0.035	0.8	0.2	2.0	77.4	31.3	94.4	0.004
HRV $10^{5.8}$	512	2	306.4	0.007	0.002	0.026	0.4	0.0	1.4	88.8	53.1	98.7	<0.001
Pooled HRV Groups	1527	14	915.6	0.015	0.009	0.026	0.9	0.5	1.5	73.7	44.0	87.9	<0.001
Placebo	517	18	305.4	0.059	0.037	0.094	3.5	2.1	5.4	-	-	-	-
G9													
HRV $10^{4.7}$	507	4	305.8	0.013	0.005	0.035	0.8	0.2	2.0	76.0	26.4	94.1	0.007
HRV $10^{5.2}$	508	6	303.6	0.020	0.009	0.044	1.2	0.4	2.6	64.1	4.5	88.4	0.033
HRV $10^{5.8}$	512	3	306.5	0.010	0.003	0.030	0.6	0.1	1.7	82.2	38.4	96.7	0.002
Pooled HRV Groups	1527	13	915.9	0.014	0.008	0.024	0.9	0.5	1.5	74.1	43.4	88.4	<0.001
Placebo	517	17	304.4	0.056	0.035	0.090	3.3	1.9	5.2	-	-	-	-
Pooled Non G1 (G2, G3, G4, G9)													
HRV $10^{4.7}$	507	5	305.8	0.016	0.007	0.039	1.0	0.3	2.3	75.7	33.8	92.8	0.002
HRV $10^{5.2}$	508	6	303.6	0.020	0.009	0.044	1.2	0.4	2.6	70.9	25.5	90.4	0.005
HRV $10^{5.8}$	512	3	306.5	0.010	0.003	0.030	0.6	0.1	1.7	85.6	51.7	97.2	<0.001
Pooled HRV Groups	1527	14	915.9	0.015	0.009	0.026	0.9	0.5	1.5	77.4	53.5	89.4	<0.001
Placebo	517	21	303.5	0.069	0.045	0.106	4.1	2.5	6.1	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one severe RV GE episode in each group
T = sum of follow-up period expressed in year censored at the first occurrence of severe RV GE episode in the first efficacy follow-up period, in each group
% = percentage of subjects reporting at least one severe RV GE episode in each group
n/T = person-year rate of severe RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 38: Percentage of subjects hospitalized due to RV GE episodes and efficacy of the vaccine from 2 weeks after Dose 2 up to the end of the first efficacy period (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**P-value**
HRV $10^{4.7}$	507	5	305.6	0.016	0.007	0.039	1.0	0.3	2.3	68.1	9.0	90.9	0.025
HRV $10^{5.2}$	508	1	305.5	0.003	0.000	0.023	0.2	0.0	1.1	93.6	59.1	99.8	<0.001
HRV $10^{5.8}$	512	3	306.3	0.010	0.003	0.030	0.6	0.1	1.7	81.1	33.9	96.5	0.004
Pooled HRV Groups	1527	9	917.4	0.010	0.005	0.019	0.6	0.3	1.1	81.0	54.2	92.6	<0.001
Placebo	517	16	305.3	0.052	0.032	0.086	3.1	1.8	5.0	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects hospitalized due to RV GE in each group
T = sum of follow-up period expressed in year censored at the first occurrence of hospitalization due to RV GE episode in the first efficacy follow-up period, in each group
n/N = percentage of subjects hospitalized due to RV GE in each group
n/T = person-year rate of hospitalization due to RV GE in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 39: Percentage of vaccinees reporting RV GE episodes from 2 weeks after Dose 2 up to the end of the first efficacy period, by status of anti-rotavirus IgA antibody concentration at two months after Dose 2 (total vaccinated cohort for efficacy for subset planned to receive two doses of study vaccine)

Anti-rotavirus	HRV $10^{4.7}$					HRV $10^{5.2}$				
Antibody status				95%CI					95%CI	
At Visit 3	N	n	%	LL	UL	N	n	%	LL	UL
Negative	70	8	11.4	5.1	21.3	58	6	10.3	3.9	21.2
Positive	110	1	0.9	0.0	5.0	107	2	1.9	0.2	6.6
Unknown	327	13	4.0	2.1	6.7	343	14	4.1	2.2	6.8

Anti-rotavirus	HRV $10^{5.8}$					Pooled HRV groups				
Antibody status				95%CI					95%CI	
At Visit 3	N	n	%	LL	UL	N	n	%	LL	UL
Negative	55	6	10.9	4.1	22.3	183	20	10.9	6.8	16.4
Positive	118	2	1.7	0.2	6.0	335	5	1.5	0.5	3.4
Unknown	339	7	2.1	0.8	4.2	1009	34	3.4	2.3	4.7

Notes: N = number of subjects included in the vaccine group with the specified status for anti-rotavirus IgA antibody concentration two months after Dose 2
n/%= number/percentage of subject with the specified status for anti-rotavirus IgA antibody concentration two months after Dose 2 reporting at least one RV GE episode from 2 weeks after Dose 2 up to the end of the first efficacy period
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 40: Percentage of subjects who reported any or severe RV GE episode(s) from day of Dose 1 till Day 14 after Dose 2 (total vaccinated cohort for subset planned to receive two doses of study vaccine)

Group	N	n	%	95%CI LL	UL
Any RV GE					
HRV $10^{4.7}$	538	14	2.6	1.4	4.3
HRV $10^{5.2}$	540	11	2.0	1.0	3.6
HRV $10^{5.8}$	540	11	2.0	1.0	3.6
Pooled HRV Groups	1618	36	2.2	1.6	3.1
Placebo	537	20	3.7	2.3	5.7
Severe RV GE					
HRV $10^{4.7}$	538	5	0.9	0.3	2.2
HRV $10^{5.2}$	540	4	0.7	0.2	1.9
HRV $10^{5.8}$	540	2	0.4	0.0	1.3
Pooled HRV Groups	1618	11	0.7	0.3	1.2
Placebo	537	10	1.9	0.9	3.4

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of specified intensity in each group
% = percentage of subjects reporting at least one RV GE episode of specified intensity in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 41: Percentage of subjects who reported any or severe RV GE episode(s) other than vaccine strain and efficacy of the vaccine from day of Dose 1 till Day 14 after Dose 2 (total vaccinated cohort for subset planned to receive two doses of study vaccine)

		n/N				Vaccine Efficacy		
				95%CI			95%CI	
Group	**N**	**n**	**%**	**LL**	**UL**	**%**	**LL**	**UL**
Any RV GE								
HRV $10^{4.7}$	538	10	1.9	0.9	3.4	50.1	-11.7	79.1
HRV $10^{5.2}$	540	6	1.1	0.4	2.4	70.2	23.0	90.2
HRV $10^{5.8}$	540	6	1.1	0.4	2.4	70.2	23.0	90.2
Pooled HRV Groups	1618	22	1.4	0.9	2.1	63.5	29.5	81.0
Placebo	537	20	3.7	2.3	5.7	-	-	-
Severe RV GE								
HRV $10^{4.7}$	538	5	0.9	0.3	2.2	50.1	-60.3	86.6
HRV $10^{5.2}$	540	2	0.4	0.0	1.3	80.1	6.7	97.9
HRV $10^{5.8}$	540	1	0.2	0.0	1.0	90.1	30.1	99.8
Pooled HRV Groups	1618	8	0.5	0.2	1.0	73.4	25.3	90.9
Placebo	537	10	1.9	0.9	3.4	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode other than vaccine strain of specified intensity in each group
% = percentage of subjects reporting at least one RV GE episode other than vaccine strain of specified intensity in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 42: Percentage of subjects who reported any or severe RV GE episode(s) and efficacy of the vaccine from day of Dose 1 till the end of the first efficacy follow-up period (total vaccinated cohort for subset planned to receive two doses of study vaccine)

				n/T			n/N			Vaccine Efficacy			
			T		95%CI			95%CI			95%CI		
Group	**N**	**n**	**(year)**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**p-value**
Any RV GE													
HRV $10^{4.7}$	538	32	410.6	0.078	0.055	0.110	5.9	4.1	8.3	57.4	34.8	72.8	<0.001
HRV $10^{5.2}$	540	28	412.6	0.068	0.047	0.098	5.2	3.5	7.4	62.9	42.0	76.8	<0.001
HRV $10^{5.8}$	540	21	417.7	0.050	0.033	0.077	3.9	2.4	5.9	72.2	54.3	83.7	<0.001
Pooled HRV Groups	1618	81	1240.9	0.065	0.052	0.081	5.0	4.0	6.2	64.2	50.3	74.1	<0.001
Placebo	537	75	399.7	0.188	0.147	0.233	14.0	11.1	17.2	-	-	-	-
Severe RV GE													
HRV $10^{4.7}$	538	18	417.8	0.043	0.027	0.068	3.3	2.0	5.2	64.1	37.3	80.3	<0.001
HRV $10^{5.2}$	540	12	420.1	0.029	0.016	0.050	2.2	1.2	3.8	76.1	54.5	88.4	<0.001
HRV $10^{5.8}$	540	6	425.3	0.014	0.006	0.031	1.1	0.4	2.4	88.1	72.2	95.8	<0.001
Pooled HRV Groups	1618	36	1263.1	0.029	0.021	0.040	2.2	1.6	3.1	76.1	62.6	84.9	<0.001
Placebo	537	50	412.3	0.121	0.092	0.160	9.3	7.0	12.1	-	-	-	-

Notes: N = number of subjects included in each group
n = number of subjects reporting at least one RV GE episode of specified intensity in each group
T = sum of follow-up period expressed in year censored at the first occurrence of RV GE episode of specified intensity in each group
% = percentage of subjects reporting at least one RV GE episode of specified intensity in each group
n/T = person-year rate of RV GE of specified intensity in each group
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
p-value = two-sided Fisher's exact test (significant level of α=0.05)

Supplement 43: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	538	114	21.2	17.8	24.9
	HRV_5.2	540	128	23.7	20.2	27.5
	HRV_5.8	540	140	25.9	22.3	29.8
	Pooled HRV groups	1618	382	23.6	21.6	25.8
	Placebo	537	129	24.0	20.5	27.9
Dose 2	**HRV_4.7**	510	105	20.6	17.2	24.4
	HRV_5.2	509	111	21.8	18.3	25.7
	HRV_5.8	515	114	22.1	18.6	26.0
	Pooled HRV groups	1534	330	21.5	19.5	23.7
	Placebo	522	104	19.9	16.6	23.6
Overall/dose	**HRV_4.7**	1048	219	20.9	18.5	23.5
	HRV_5.2	1049	239	22.8	20.3	25.4
	HRV_5.8	1055	254	24.1	21.5	26.8
	Pooled HRV groups	3152	712	22.6	21.1	24.1
	Placebo	1059	233	22.0	19.5	24.6
Overall/subject	**HRV_4.7**	538	180	33.5	29.5	37.6
	HRV_5.2	540	204	37.8	33.7	42.0
	HRV_5.8	540	196	36.3	32.2	40.5
	Pooled HRV groups	1618	580	35.8	33.5	38.2
	Placebo	537	190	35.4	31.3	39.6

Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N = number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom

Supplement 44: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15- day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	538	275	51.1	46.8	55.4
	HRV_5.2	540	278	51.5	47.2	55.8
	HRV_5.8	540	271	50.2	45.9	54.5
	Pooled HRV groups	1618	824	50.9	48.5	53.4
	Placebo	537	276	51.4	47.1	55.7
Dose 2	**HRV_4.7**	510	218	42.7	38.4	47.2
	HRV_5.2	509	234	46.0	41.6	50.4
	HRV_5.8	515	240	46.6	42.2	51.0
	Pooled HRV groups	1534	692	45.1	42.6	47.6
	Placebo	522	223	42.7	38.4	47.1
Overall/dose	**HRV_4.7**	1048	493	47.0	44.0	50.1
	HRV_5.2	1049	512	48.8	45.7	51.9
	HRV_5.8	1055	511	48.4	45.4	51.5
	Pooled HRV groups	3152	1516	48.1	46.3	49.9
	Placebo	1059	499	47.1	44.1	50.2
Overall/subject	**HRV_4.7**	538	285	53.0	48.7	57.3
	HRV_5.2	540	289	53.5	49.2	57.8
	HRV_5.8	540	287	53.1	48.8	57.4
	Pooled HRV groups	1618	861	53.2	50.7	55.7
	Placebo	537	281	52.3	48.0	56.6

Notes: exact 95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N = number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom

Supplement 45: Percentage of doses and subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/Dose											
Group		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		1048				1049				1055			
COUGH	Total	635	60.6	57.6	63.6	639	60.9	57.9	63.9	656	62.2	59.2	65.1
	Grade 2*3	335	32.0	29.1	34.9	313	29.8	27.1	32.7	343	32.5	29.7	35.4
	Grade 3	96	9.2	7.5	11.1	102	9.7	8.0	11.7	109	10.3	8.6	12.3
	Related	206	19.7	17.3	22.2	212	20.2	17.8	22.8	200	19.0	16.6	21.5
DIARRHEA	Total	71	6.8	5.3	8.5	68	6.5	5.1	8.1	88	8.3	6.7	10.2
	Grade 2*3	48	4.6	3.4	6.0	47	4.5	3.3	5.9	57	5.4	4.1	6.9
	Grade 3	16	1.5	0.9	2.5	23	2.2	1.4	3.3	24	2.3	1.5	3.4
	Related	35	3.3	2.3	4.6	43	4.1	3.0	5.5	50	4.7	3.5	6.2
IRRITABILITY	Total	673	64.2	61.2	67.1	683	65.1	62.1	68.0	704	66.7	63.8	69.6
	Grade 2*3	414	39.5	36.5	42.5	407	38.8	35.8	41.8	450	42.7	39.6	45.7
	Grade 3	118	11.3	9.4	13.3	112	10.7	8.9	12.7	124	11.8	9.9	13.9
	Related	404	38.5	35.6	41.6	400	38.1	35.2	41.1	418	39.6	36.7	42.6
LOSS OF APPETITE	Total	319	30.4	27.7	33.3	322	30.7	27.9	33.6	323	30.6	27.8	33.5
	Grade 2*3	117	11.2	9.3	13.2	112	10.7	8.9	12.7	131	12.4	10.5	14.6
	Grade 3	20	1.9	1.2	2.9	23	2.2	1.4	3.3	15	1.4	0.8	2.3
	Related	133	12.7	10.7	14.9	132	12.6	10.6	14.7	131	12.4	10.5	14.6
FEVER	Total	606	57.8	54.8	60.8	611	58.2	55.2	61.3	611	57.9	54.9	60.9
	Grade 2*3	233	22.2	19.7	24.9	226	21.5	19.1	24.2	240	22.7	20.3	25.4
	Grade 3	15	1.4	0.8	2.3	20	1.9	1.2	2.9	22	2.1	1.3	3.1
	Related	344	32.8	30.0	35.8	316	30.1	27.4	33.0	332	31.5	28.7	34.4
VOMITING	Total	143	13.6	11.6	15.9	175	16.7	14.5	19.1	156	14.8	12.7	17.1
	Grade 2*3	62	5.9	4.6	7.5	102	9.7	8.0	11.7	80	7.6	6.1	9.3
	Grade 3	25	2.4	1.5	3.5	46	4.4	3.2	5.8	42	4.0	2.9	5.3
	Related	80	7.6	6.1	9.4	79	7.5	6.0	9.3	63	6.0	4.6	7.6

Notes: exact 95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination

Supplement 45(continued): Percentage of doses and subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/Dose							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		3152				1059			
COUGH	Total	1930	61.2	59.5	62.9	671	63.4	60.4	66.3
	Grade 2*3	991	31.4	29.8	33.1	372	35.1	32.2	38.1
	Grade 3	307	9.7	8.7	10.8	80	7.6	6.0	9.3
	Related	618	19.6	18.2	21.0	208	19.6	17.3	22.2
DIARRHEA	Total	227	7.2	6.3	8.2	91	8.6	7.0	10.4
	Grade 2*3	152	4.8	4.1	5.6	60	5.7	4.4	7.2
	Grade 3	63	2.0	1.5	2.6	25	2.4	1.5	3.5
	Related	128	4.1	3.4	4.8	43	4.1	3.0	5.4
IRRITABILITY	Total	2060	65.4	63.7	67.0	713	67.3	64.4	70.1
	Grade 2*3	1271	40.3	38.6	42.1	449	42.4	39.4	45.4
	Grade 3	354	11.2	10.1	12.4	124	11.7	9.8	13.8
	Related	1222	38.8	37.1	40.5	407	38.4	35.5	41.4
LOSS OF APPETITE	Total	964	30.6	29.0	32.2	336	31.7	28.9	34.6
	Grade 2*3	360	11.4	10.3	12.6	134	12.7	10.7	14.8
	Grade 3	58	1.8	1.4	2.4	20	1.9	1.2	2.9
	Related	396	12.6	11.4	13.8	145	13.7	11.7	15.9
FEVER	Total	1828	58.0	56.2	59.7	634	59.9	56.8	62.8
	Grade 2*3	699	22.2	20.7	23.7	222	21.0	18.5	23.5
	Grade 3	57	1.8	1.4	2.3	22	2.1	1.3	3.1
	Related	992	31.5	29.9	33.1	317	29.9	27.2	32.8
VOMITING	Total	474	15.0	13.8	16.3	148	14.0	11.9	16.2
	Grade 2*3	244	7.7	6.8	8.7	73	6.9	5.4	8.6
	Grade 3	113	3.6	3.0	4.3	28	2.6	1.8	3.8
	Related	222	7.0	6.2	8.0	78	7.4	5.9	9.1

Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination

Supplement 45(continued): Percentage of doses and subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/Subject											
Group		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		538				540				540			
COUGH	Total	420	78.1	74.3	81.5	420	77.8	74.0	81.2	423	78.3	74.6	81.7
	Grade 2*3	247	45.9	41.6	50.2	249	46.1	41.8	50.4	258	47.8	43.5	52.1
	Grade 3	88	16.4	13.3	19.8	91	16.9	13.8	20.3	92	17.0	14.0	20.5
	Related	157	29.2	25.4	33.2	168	31.1	27.2	35.2	164	30.4	26.5	34.4
DIARRHEA	Total	68	12.6	10.0	15.7	61	11.3	8.8	14.3	77	14.3	11.4	17.5
	Grade 2*3	46	8.6	6.3	11.2	45	8.3	6.1	11.0	52	9.6	7.3	12.4
	Grade 3	16	3.0	1.7	4.8	23	4.3	2.7	6.3	23	4.3	2.7	6.3
	Related	35	6.5	4.6	8.9	41	7.6	5.5	10.2	45	8.3	6.1	11.0
IRRITABILITY	Total	422	78.4	74.7	81.8	436	80.7	77.2	84.0	441	81.7	78.1	84.8
	Grade 2*3	305	56.7	52.4	60.9	305	56.5	52.2	60.7	318	58.9	54.6	63.1
	Grade 3	97	18.0	14.9	21.5	97	18.0	14.8	21.5	95	17.6	14.5	21.1
	Related	254	47.2	42.9	51.5	252	46.7	42.4	51.0	267	49.4	45.1	53.7
LOSS OF APPETITE	Total	240	44.6	40.4	48.9	246	45.6	41.3	49.9	241	44.6	40.4	48.9
	Grade 2*3	103	19.1	15.9	22.7	98	18.1	15.0	21.7	111	20.6	17.2	24.2
	Grade 3	18	3.3	2.0	5.2	21	3.9	2.4	5.9	15	2.8	1.6	4.5
	Related	109	20.3	16.9	23.9	108	20.0	16.7	23.6	104	19.3	16.0	22.8
FEVER	Total	410	76.2	72.4	79.7	422	78.1	74.4	81.6	406	75.2	71.3	78.8
	Grade 2*3	194	36.1	32.0	40.3	195	36.1	32.1	40.3	198	36.7	32.6	40.9
	Grade 3	15	2.8	1.6	4.6	20	3.7	2.3	5.7	21	3.9	2.4	5.9
	Related	236	43.9	39.6	48.2	223	41.3	37.1	45.6	224	41.5	37.3	45.8
VOMITING	Total	122	22.7	19.2	26.5	148	27.4	23.7	31.4	133	24.6	21.1	28.5
	Grade 2*3	54	10.0	7.6	12.9	91	16.9	13.8	20.3	74	13.7	10.9	16.9
	Grade 3	24	4.5	2.9	6.6	44	8.1	6.0	10.8	39	7.2	5.2	9.7
	Related	68	12.6	10.0	15.7	70	13.0	10.2	16.1	56	10.4	7.9	13.3

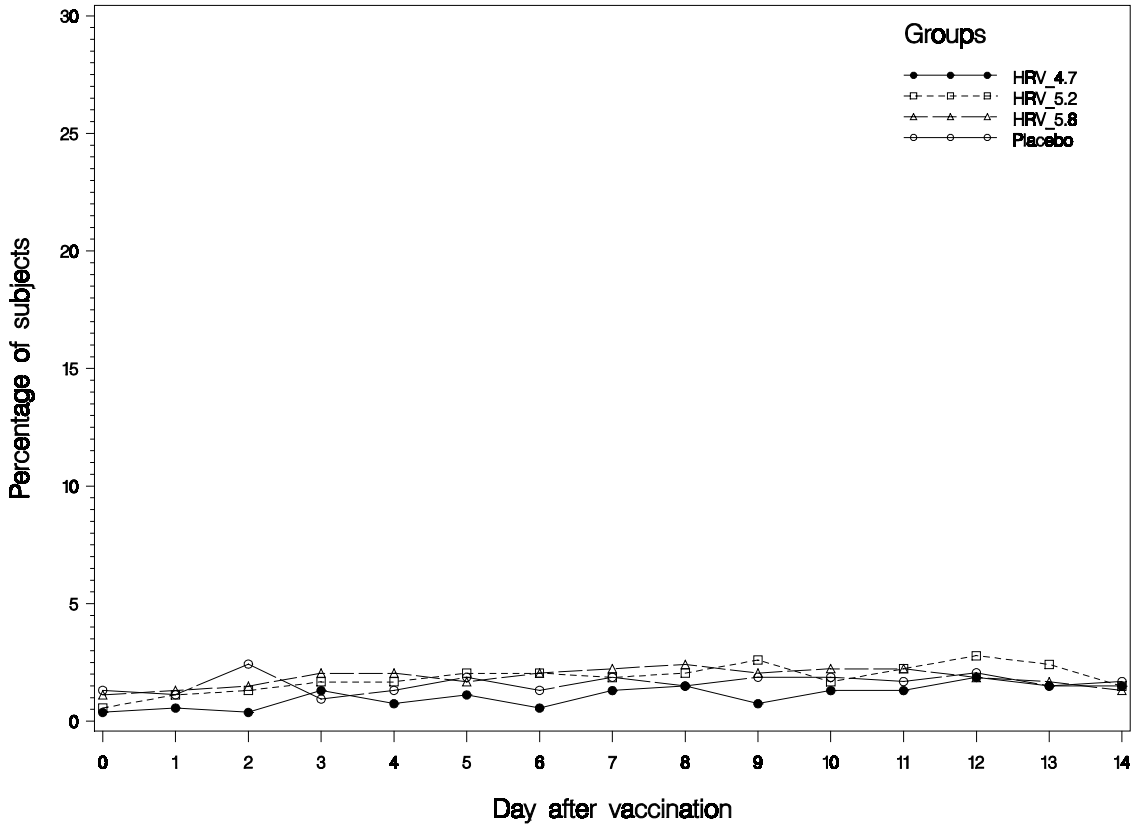
Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination

Supplement 45(continued): Percentage of doses and subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/subject							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		1618				537			
COUGH	Total	1263	78.1	76.0	80.1	437	81.4	77.8	84.6
	Grade 2*3	754	46.6	44.1	49.1	287	53.4	49.1	57.7
	Grade 3	271	16.7	15.0	18.7	71	13.2	10.5	16.4
	Related	489	30.2	28.0	32.5	162	30.2	26.3	34.2
DIARRHEA	Total	206	12.7	11.1	14.5	85	15.8	12.8	19.2
	Grade 2*3	143	8.8	7.5	10.3	58	10.8	8.3	13.7
	Grade 3	62	3.8	3.0	4.9	23	4.3	2.7	6.4
	Related	121	7.5	6.2	8.9	41	7.6	5.5	10.2
IRRITABILITY	Total	1299	80.3	78.3	82.2	444	82.7	79.2	85.8
	Grade 2*3	928	57.4	54.9	59.8	328	61.1	56.8	65.2
	Grade 3	289	17.9	16.0	19.8	109	20.3	17.0	24.0
	Related	773	47.8	45.3	50.2	258	48.0	43.7	52.4
LOSS OF APPETITE	Total	727	44.9	42.5	47.4	252	46.9	42.6	51.2
	Grade 2*3	312	19.3	17.4	21.3	113	21.0	17.7	24.7
	Grade 3	54	3.3	2.5	4.3	20	3.7	2.3	5.7
	Related	321	19.8	17.9	21.9	118	22.0	18.5	25.7
FEVER	Total	1238	76.5	74.4	78.6	425	79.1	75.5	82.5
	Grade 2*3	587	36.3	33.9	38.7	184	34.3	30.3	38.4
	Grade 3	56	3.5	2.6	4.5	21	3.9	2.4	5.9
	Related	683	42.2	39.8	44.7	224	41.7	37.5	46.0
VOMITING	Total	403	24.9	22.8	27.1	129	24.0	20.5	27.9
	Grade 2*3	219	13.5	11.9	15.3	67	12.5	9.8	15.6
	Grade 3	107	6.6	5.5	7.9	27	5.0	3.3	7.2
	Related	194	12.0	10.4	13.7	70	13.0	10.3	16.2

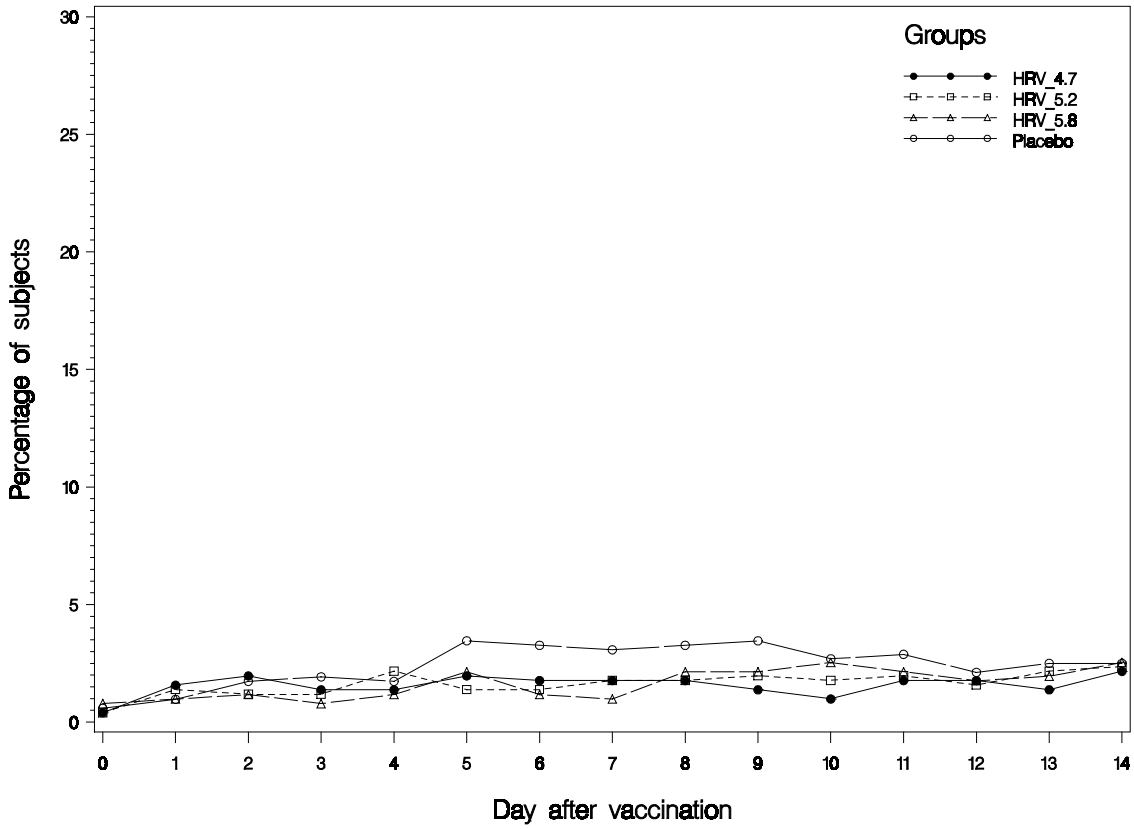
Notes: 95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination

Supplement 46: Prevalence of diarrhea by day after vaccination, during the solicited 15-day follow-up period after Dose 1 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



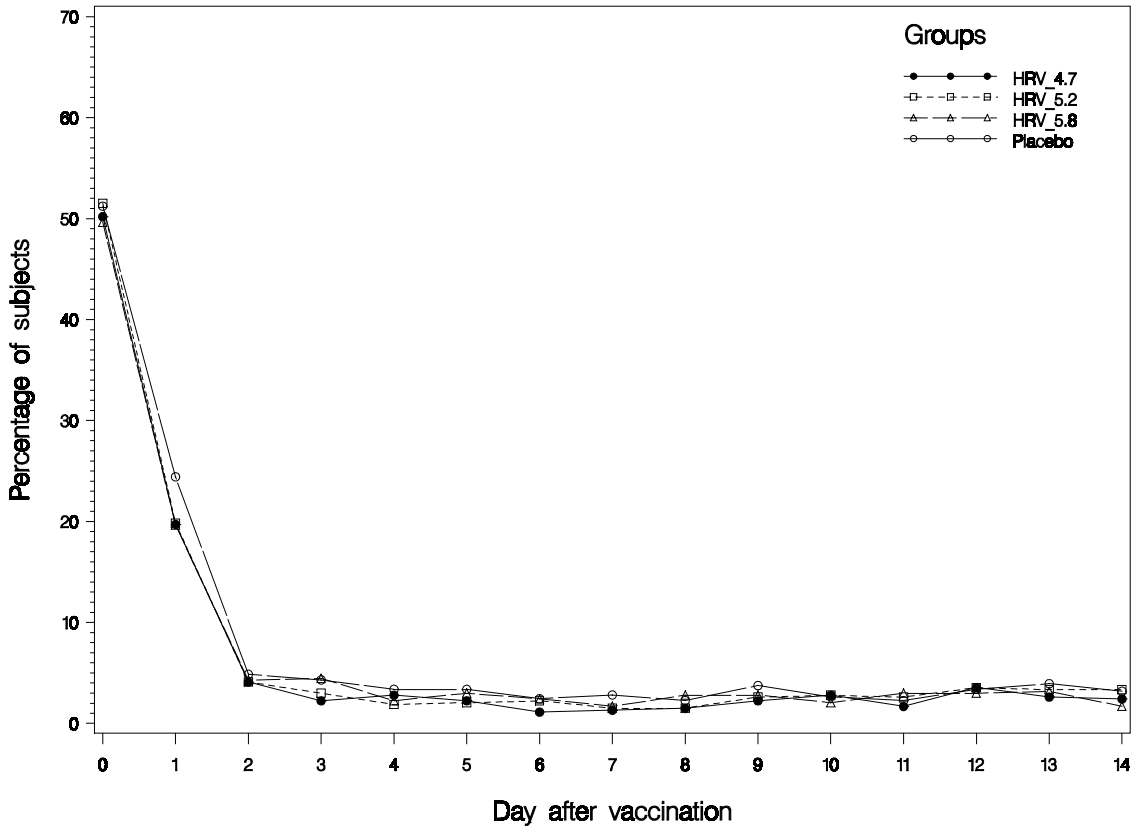
Notes: D0 = day of vaccination, D1 = on day after vaccination,…

Supplement 47: Prevalence of diarrhea by day after vaccination, during the solicited 15-day follow-up period after Dose 2 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



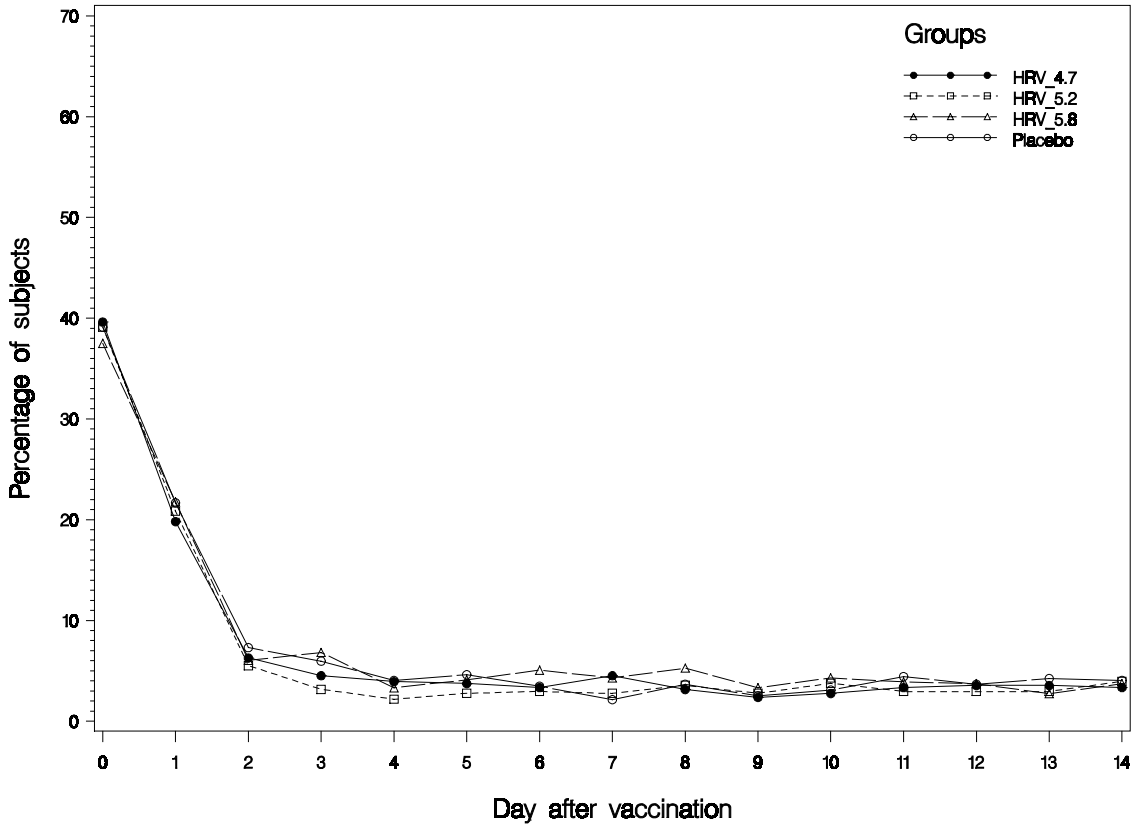
Notes: D0 = day of vaccination, D1 = on day after vaccination,…

Supplement 48: Prevalence of fever by day after vaccination, during the solicited 15-day follow-up period after Dose 1 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



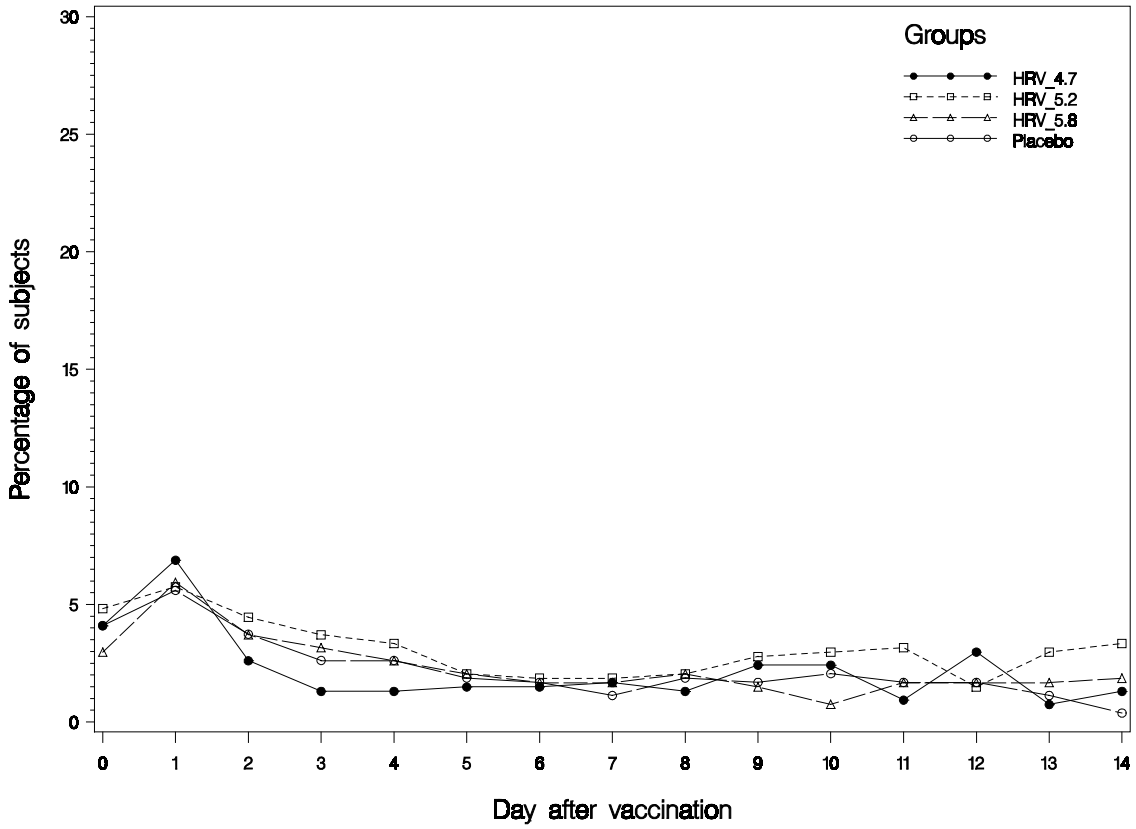
Notes: D0 = day of vaccination, D1 = on day after vaccination,…

Supplement 49: Prevalence of fever by day after vaccination, during the solicited 15-day follow-up period after Dose 2 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



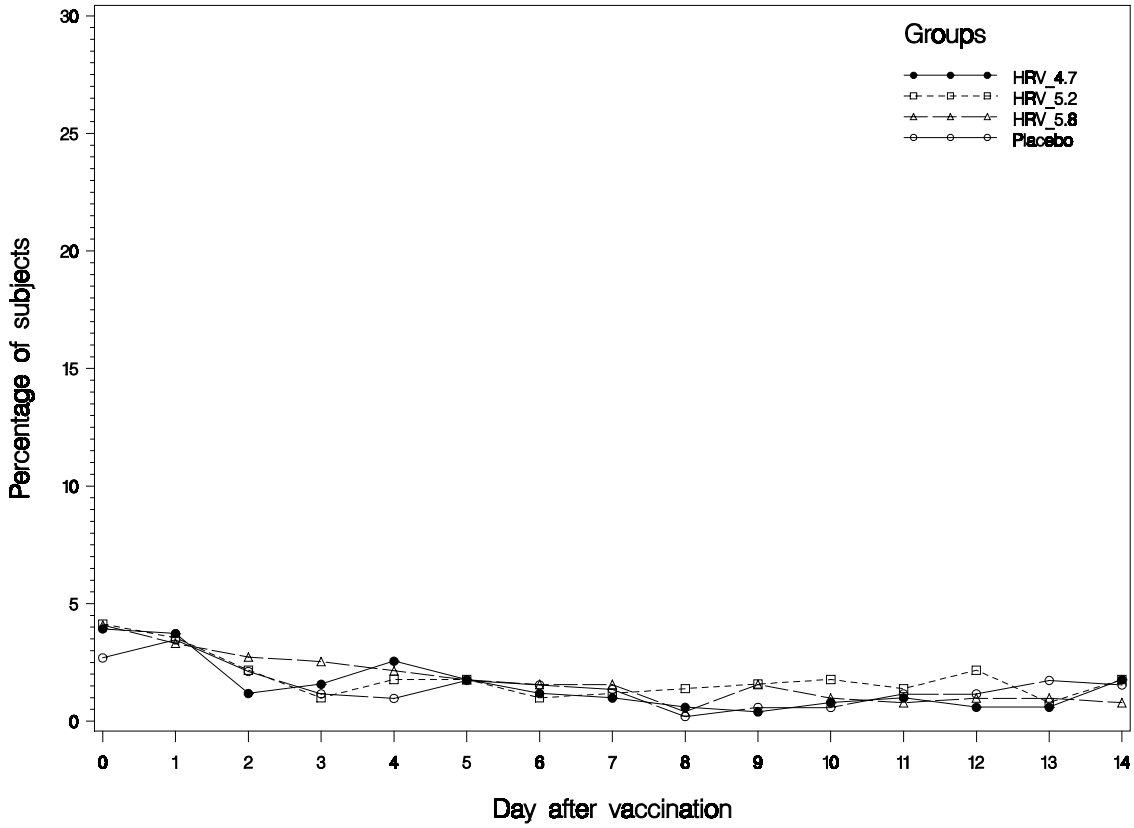
Notes: D0 = day of vaccination, D1 = on day after vaccination,…

Supplement 50: Prevalence of vomiting by day after vaccination, during the solicited 15-day follow-up period after Dose 1 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



Notes: D0 = day of vaccination, D1 = on day after vaccination

Supplement 51: Prevalence of vomiting by day after vaccination, during the solicited 15-day follow-up period after Dose 2 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



Notes: D0 = day of vaccination, D1 = on day after vaccination

Supplement 52: Duration (in days) of diarrhea, vomiting and fever during the solicited 15-day follow-up period (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Solicited symptom	Dose	Group	n	Mean	Min	Q1	Median	Q3	Max
Fever	Dose 1	HRV_4.7	331	1.6	1.0	1.0	1.0	2.0	8.0
		HRV_5.2	339	1.7	1.0	1.0	1.0	2.0	12.0
		HRV_5.8	331	1.7	1.0	1.0	1.0	2.0	8.0
		Pooled HRV groups	1001	1.7	1.0	1.0	1.0	2.0	12.0
		Placebo	346	1.8	1.0	1.0	1.0	2.0	15.0
	Dose 2	HRV_4.7	275	2.0	1.0	1.0	2.0	2.0	11.0
		HRV_5.2	272	1.9	1.0	1.0	1.0	2.0	12.0
		HRV_5.8	279	2.1	1.0	1.0	2.0	3.0	9.0
		Pooled HRV groups	826	2.0	1.0	1.0	2.0	2.0	12.0
		Placebo	288	2.1	1.0	1.0	2.0	2.0	9.0
	All/Dose	HRV_4.7	606	1.8	1.0	1.0	1.0	2.0	11.0
		HRV_5.2	611	1.8	1.0	1.0	1.0	2.0	12.0
		HRV_5.8	610	1.9	1.0	1.0	1.0	2.0	9.0
		Pooled HRV groups	1827	1.8	1.0	1.0	1.0	2.0	12.0
		Placebo	634	1.9	1.0	1.0	1.5	2.0	15.0
Vomiting	Dose 1	HRV_4.7	88	2.0	1.0	1.0	1.0	2.0	14.0
		HRV_5.2	106	2.4	1.0	1.0	1.0	3.0	12.0
		HRV_5.8	90	2.1	1.0	1.0	2.0	3.0	6.0
		Pooled HRV groups	284	2.2	1.0	1.0	1.0	2.0	14.0
		Placebo	89	2.0	1.0	1.0	1.0	2.0	11.0
	Dose 2	HRV_4.7	55	2.1	1.0	1.0	1.0	3.0	8.0
		HRV_5.2	69	2.0	1.0	1.0	1.0	3.0	6.0
		HRV_5.8	65	2.1	1.0	1.0	1.0	3.0	8.0
		Pooled HRV groups	189	2.1	1.0	1.0	1.0	3.0	8.0
		Placebo	59	1.9	1.0	1.0	1.0	2.0	7.0
	All/Dose	HRV_4.7	143	2.0	1.0	1.0	1.0	2.0	14.0
		HRV_5.2	175	2.2	1.0	1.0	1.0	3.0	12.0
		HRV_5.8	155	2.1	1.0	1.0	2.0	3.0	8.0
		Pooled HRV groups	473	2.1	1.0	1.0	1.0	3.0	14.0
		Placebo	148	2.0	1.0	1.0	1.0	2.0	11.0
Diarrhea	Dose 1	HRV_4.7	33	2.6	1.0	1.0	2.0	3.0	9.0
		HRV_5.2	34	4.4	1.0	2.0	3.0	6.0	14.0
		HRV_5.8	44	3.4	1.0	1.0	2.0	5.0	11.0
		Pooled HRV groups	111	3.5	1.0	1.0	2.0	5.0	14.0
		Placebo	45	2.9	1.0	1.0	2.0	4.0	12.0
	Dose 2	HRV_4.7	38	3.1	1.0	1.0	2.0	5.0	12.0
		HRV_5.2	34	3.6	1.0	1.0	3.0	5.0	13.0
		HRV_5.8	44	2.8	1.0	1.0	2.0	4.0	11.0
		Pooled HRV groups	116	3.2	1.0	1.0	2.0	5.0	13.0
		Placebo	46	4.1	1.0	1.0	3.5	6.0	13.0
	All/Dose	HRV_4.7	71	2.9	1.0	1.0	2.0	4.0	12.0
		HRV_5.2	68	4.0	1.0	1.0	3.0	6.0	14.0
		HRV_5.8	88	3.1	1.0	1.0	2.0	5.0	11.0
		Pooled HRV groups	227	3.3	1.0	1.0	2.0	5.0	14.0
		Placebo	91	3.5	1.0	1.0	3.0	5.0	13.0

Notes: n = number of doses reporting the specified solicited symptom
Q1 = 25th percentile
Q3 = 75th percentile

Supplement 53: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 538				HRV_5.2 N = 540				HRV_5.8 N = 540				Pooled HRV groups N = 1618				Placebo N = 537			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		350	65.1	60.9	69.1	354	65.6	61.4	69.6	328	60.7	56.5	64.9	1032	63.8	61.4	66.1	342	63.7	59.5	67.8
Application site (1820)	Dermatitis contact (0049)	4	0.7	0.2	1.9	8	1.5	0.6	2.9	4	0.7	0.2	1.9	16	1	0.6	1.6	6	1.1	0.4	2.4
	Injection site reaction (0058)	7	1.3	0.5	2.7	5	0.9	0.3	2.1	5	0.9	0.3	2.1	17	1.1	0.6	1.7	7	1.3	0.5	2.7
	Otitis externa (0059)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1	1	0.1	0	0.3	0	0	0	0.7
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.7	2	0.4	0	1.3	1	0.2	0	1	3	0.2	0	0.5	1	0.2	0	1
	Allergic reaction (0712)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	3	0.6	0.1	1.6
	Allergy (1058)	3	0.6	0.1	1.6	12	2.2	1.2	3.8	6	1.1	0.4	2.4	21	1.3	0.8	2	9	1.7	0.8	3.2
	Death, nos (0722)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1	1	0.1	0	0.3	0	0	0	0.7
	Edema generalised (0400)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
	Fever (0725)	44	8.2	6	10.8	44	8.1	6	10.8	45	8.3	6.1	11	133	8.2	6.9	9.7	41	7.6	5.5	10.2
	Injury (9001)	5	0.9	0.3	2.2	0	0	0	0.7	0	0	0	0.7	5	0.3	0.1	0.7	0	0	0	0.7
	Pallor (0220)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
Cardiovascular general (1010)	Cyanosis (0501)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	0.7	2	0.4	0	1.3	0	0	0	0.7	2	0.1	0	0.4	1	0.2	0	1
	Fever convulsions (1357)	1	0.2	0	1	0	0	0	0.7	1	0.2	0	1	2	0.1	0	0.4	0	0	0	0.7
	Spasm generalized (0149)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
	Vascular malformation peripheral (0764)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 53 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 538				HRV_5.2 N = 540				HRV_5.8 N = 540				Pooled HRV groups N = 1618				Placebo N = 537			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Gastrointestinal system (600)	Abdominal pain (0268)	33	6.1	4.3	8.5	30	5.6	3.8	7.8	25	4.6	3	6.8	88	5.4	4.4	6.7	25	4.7	3	6.8
	Anorexia (0165)	21	3.9	2.4	5.9	21	3.9	2.4	5.9	14	2.6	1.4	4.3	56	3.5	2.6	4.5	26	4.8	3.2	7
	Anus disorder (0269)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
	Constipation (0204)	11	2	1	3.6	11	2	1	3.6	10	1.9	0.9	3.4	32	2	1.4	2.8	6	1.1	0.4	2.4
	Gastroenteritis (0293)	3	0.6	0.1	1.6	5	0.9	0.3	2.1	1	0.2	0	1	9	0.6	0.3	1.1	4	0.7	0.2	1.9
	Gastroesophageal reflux (1149)	4	0.7	0.2	1.9	7	1.3	0.5	2.7	7	1.3	0.5	2.7	18	1.1	0.7	1.8	3	0.6	0.1	1.6
	Gastrointestinal disorder nos (1262)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1	1	0.1	0	0.3	1	0.2	0	1
	Stomatitis (0327)	0	0	0	0.7	1	0.2	0	1	1	0.2	0	1	2	0.1	0	0.4	1	0.2	0	1
	Stomatitis aphthous (0751)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
	Vomiting (0228)	14	2.6	1.4	4.3	17	3.1	1.8	5	16	3	1.7	4.8	47	2.9	2.1	3.8	20	3.7	2.3	5.7
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
	Earache (0260)	2	0.4	0	1.3	1	0.2	0	1	1	0.2	0	1	4	0.2	0.1	0.6	2	0.4	0	1.3
Neoplasm (1700)	Neoplasm nos (1259)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
Psychiatric (500)	Nervousness (0188)	30	5.6	3.8	7.9	26	4.8	3.2	7	30	5.6	3.8	7.8	86	5.3	4.3	6.5	34	6.3	4.4	8.7
Red blood cell (1210)	Anemia (0544)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
Reproductive female (1420)	Leukorrhea (0654)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1	1	0.1	0	0.3	0	0	0	0.7
Resistance mechanism (1830)	Abscess (0887)	1	0.2	0	1	2	0.4	0	1.3	3	0.6	0.1	1.6	6	0.4	0.1	0.8	0	0	0	0.7
	Infection (0736)	26	4.8	3.2	7	22	4.1	2.6	6.1	18	3.3	2	5.2	66	4.1	3.2	5.2	24	4.5	2.9	6.6
	Infection bacterial (0738)	1	0.2	0	1	2	0.4	0	1.3	0	0	0	0.7	3	0.2	0	0.5	1	0.2	0	1

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 53 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 538				HRV_5.2 N = 540				HRV_5.8 N = 540				Pooled HRV groups N = 1618				Placebo N = 537			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
	Infection viral (0740)	171	31.8	27.9	35.9	160	29.6	25.8	33.7	155	28.7	24.9	32.7	486	30	27.8	32.3	171	31.8	27.9	36
	Moniliasis (0741)	7	1.3	0.5	2.7	12	2.2	1.2	3.8	3	0.6	0.1	1.6	22	1.4	0.9	2.1	5	0.9	0.3	2.2
	Otitis media (0750)	5	0.9	0.3	2.2	11	2	1	3.6	3	0.6	0.1	1.6	19	1.2	0.7	1.8	11	2	1	3.6
	Upper resp tract infection (0543)	41	7.6	5.5	10.2	36	6.7	4.7	9.1	44	8.1	6	10.8	121	7.5	6.2	8.9	40	7.4	5.4	10
Respiratory system (1100)	Asthma (1367)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
	Atelectasis (1197)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
	Bronchitis (0805)	21	3.9	2.4	5.9	30	5.6	3.8	7.8	21	3.9	2.4	5.9	72	4.4	3.5	5.6	14	2.6	1.4	4.3
	Bronchospasm (0511)	14	2.6	1.4	4.3	9	1.7	0.8	3.1	12	2.2	1.2	3.8	35	2.2	1.5	3	7	1.3	0.5	2.7
	Coughing (0513)	30	5.6	3.8	7.9	25	4.6	3	6.8	29	5.4	3.6	7.6	84	5.2	4.2	6.4	20	3.7	2.3	5.7
	Dyspnea (0514)	0	0	0	0.7	1	0.2	0	1	1	0.2	0	1	2	0.1	0	0.4	1	0.2	0	1
	Laryngitis (0521)	1	0.2	0	1	3	0.6	0.1	1.6	2	0.4	0	1.3	6	0.4	0.1	0.8	2	0.4	0	1.3
	Pharyngitis (0523)	59	11	8.5	13.9	74	13.7	10.9	16.9	64	11.9	9.2	14.9	197	12.2	10.6	13.9	70	13	10.3	16.2
	Pneumonia (0528)	14	2.6	1.4	4.3	25	4.6	3	6.8	20	3.7	2.3	5.7	59	3.6	2.8	4.7	20	3.7	2.3	5.7
	Respiratory disorder (0536)	0	0	0	0.7	6	1.1	0.4	2.4	1	0.2	0	1	7	0.4	0.2	0.9	2	0.4	0	1.3
	Rhinitis (0539)	9	1.7	0.8	3.2	15	2.8	1.6	4.5	12	2.2	1.2	3.8	36	2.2	1.6	3.1	14	2.6	1.4	4.3
	Sputum increased (0541)	3	0.6	0.1	1.6	8	1.5	0.6	2.9	2	0.4	0	1.3	13	0.8	0.4	1.4	3	0.6	0.1	1.6
Secondary term (2000)	Varicella (1516)	2	0.4	0	1.3	1	0.2	0	1	1	0.2	0	1	4	0.2	0.1	0.6	4	0.7	0.2	1.9
Skin and appendages (100)	Alopecia (0002)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
	Dermatitis (0007)	2	0.4	0	1.3	4	0.7	0.2	1.9	5	0.9	0.3	2.1	11	0.7	0.3	1.2	0	0	0	0.7
	Dermatitis fungal (0009)	1	0.2	0	1	0	0	0	0.7	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
	Furunculosis (0016)	3	0.6	0.1	1.6	1	0.2	0	1	1	0.2	0	1	5	0.3	0.1	0.7	0	0	0	0.7

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 53 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 538				HRV_5.2 N = 540				HRV_5.8 N = 540				Pooled HRV groups N = 1618				Placebo N = 537			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
	Photosensitivity reaction (0022)	0	0	0	0.7	0	0	0	0.7	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1
	Pruritus (0024)	0	0	0	0.7	3	0.6	0.1	1.6	2	0.4	0	1.3	5	0.3	0.1	0.7	0	0	0	0.7
	Rash (0027)	1	0.2	0	1	1	0.2	0	1	0	0	0	0.7	2	0.1	0	0.4	0	0	0	0.7
	Rash erythematous (0028)	2	0.4	0	1.3	1	0.2	0	1	0	0	0	0.7	3	0.2	0	0.5	1	0.2	0	1
	Rash maculo-papular (0030)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7	1	0.1	0	0.3	1	0.2	0	1
	Rash pustular (0032)	0	0	0	0.7	2	0.4	0	1.3	3	0.6	0.1	1.6	5	0.3	0.1	0.7	2	0.4	0	1.3
	Seborrhea (0033)	0	0	0	0.7	1	0.2	0	1	0	0	0	0.7	1	0.1	0	0.3	0	0	0	0.7
	Skin disorder (0037)	6	1.1	0.4	2.4	8	1.5	0.6	2.9	9	1.7	0.8	3.1	23	1.4	0.9	2.1	10	1.9	0.9	3.4
	Sweat gland disorder (1166)	1	0.2	0	1	1	0.2	0	1	2	0.4	0	1.3	4	0.2	0.1	0.6	0	0	0	0.7
Urinary system (1300)	Dysuria (0601)	0	0	0	0.7	1	0.2	0	1	2	0.4	0	1.3	3	0.2	0	0.5	0	0	0	0.7
	Urinary tract infection (0628)	0	0	0	0.7	0	0	0	0.7	2	0.4	0	1.3	2	0.1	0	0.4	2	0.4	0	1.3
Vision (431)	Blepharitis (1007)	1	0.2	0	1	0	0	0	0.7	1	0.2	0	1	2	0.1	0	0.4	0	0	0	0.7
	Conjunctivitis (0238)	13	2.4	1.3	4.1	13	2.4	1.3	4.1	9	1.7	0.8	3.1	35	2.2	1.5	3	10	1.9	0.9	3.4
White cell and reticuloendothelial system (1220)	Lymphadenopathy cervical (0578)	0	0	0	0.7	0	0	0	0.7	1	0.2	0	1	1	0.1	0	0.3	0	0	0	0.7

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 54: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		482	46	42.9	49.1	495	47.2	44.1	50.3	460	43.6	40.6	46.7	1437	45.6	43.8	47.3	475	44.9	41.8	47.9
Application site (1820)	Dermatitis contact (0049)	4	0.4	0.1	1	8	0.8	0.3	1.5	4	0.4	0.1	1	16	0.5	0.3	0.8	7	0.7	0.3	1.4
	Injection site reaction (0058)	7	0.7	0.3	1.4	5	0.5	0.2	1.1	5	0.5	0.2	1.1	17	0.5	0.3	0.9	8	0.8	0.3	1.5
	Otitis externa (0059)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	0	0	0	0.3
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.4	2	0.2	0	0.7	1	0.1	0	0.5	3	0.1	0	0.3	1	0.1	0	0.5
	Allergic reaction (0712)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	3	0.3	0.1	0.8
	Allergy (1058)	3	0.3	0.1	0.8	14	1.3	0.7	2.2	6	0.6	0.2	1.2	23	0.7	0.5	1.1	9	0.8	0.4	1.6
	Death, nos (0722)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	0	0	0	0.3
	Edema generalised (0400)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Fever (0725)	45	4.3	3.1	5.7	46	4.4	3.2	5.8	47	4.5	3.3	5.9	138	4.4	3.7	5.2	43	4.1	3	5.4
	Injury (9001)	5	0.5	0.2	1.1	0	0	0	0.4	0	0	0	0.3	5	0.2	0.1	0.4	0	0	0	0.3
	Pallor (0220)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Cardiovascular general (1010)	Cyanosis (0501)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	0.4	2	0.2	0	0.7	0	0	0	0.3	2	0.1	0	0.2	1	0.1	0	0.5
	Fever convulsions (1357)	1	0.1	0	0.5	0	0	0	0.4	1	0.1	0	0.5	2	0.1	0	0.2	0	0	0	0.3
	Spasm generalized (0149)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Vascular malformation peripheral (0764)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 54 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Gastrointestinal system (600)	Abdominal pain (0268)	35	3.3	2.3	4.6	31	3	2	4.2	30	2.8	1.9	4	96	3	2.5	3.7	25	2.4	1.5	3.5
	Anorexia (0165)	24	2.3	1.5	3.4	23	2.2	1.4	3.3	15	1.4	0.8	2.3	62	2	1.5	2.5	27	2.5	1.7	3.7
	Anus disorder (0269)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Constipation (0204)	11	1	0.5	1.9	12	1.1	0.6	2	11	1	0.5	1.9	34	1.1	0.7	1.5	6	0.6	0.2	1.2
	Gastroenteritis (0293)	3	0.3	0.1	0.8	5	0.5	0.2	1.1	1	0.1	0	0.5	9	0.3	0.1	0.5	4	0.4	0.1	1
	Gastroesophageal reflux (1149)	4	0.4	0.1	1	7	0.7	0.3	1.4	7	0.7	0.3	1.4	18	0.6	0.3	0.9	3	0.3	0.1	0.8
	Gastrointestinal disorder nos (1262)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	1	0.1	0	0.5
	Stomatitis (0327)	0	0	0	0.4	1	0.1	0	0.5	1	0.1	0	0.5	2	0.1	0	0.2	1	0.1	0	0.5
	Stomatitis aphthous (0751)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Vomiting (0228)	14	1.3	0.7	2.2	18	1.7	1	2.7	17	1.6	0.9	2.6	49	1.6	1.2	2.1	20	1.9	1.2	2.9
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Earache (0260)	2	0.2	0	0.7	1	0.1	0	0.5	1	0.1	0	0.5	4	0.1	0	0.3	2	0.2	0	0.7
Neoplasm (1700)	Neoplasm nos (1259)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
Psychiatric (500)	Nervousness (0188)	39	3.7	2.7	5.1	30	2.9	1.9	4.1	35	3.3	2.3	4.6	104	3.3	2.7	4	37	3.5	2.5	4.8
Red blood cell (1210)	Anemia (0544)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
Reproductive female (1420)	Leukorrhea (0654)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	0	0	0	0.3
Resistance mechanism (1830)	Abscess (0887)	1	0.1	0	0.5	2	0.2	0	0.7	3	0.3	0.1	0.8	6	0.2	0.1	0.4	0	0	0	0.3
	Infection (0736)	27	2.6	1.7	3.7	23	2.2	1.4	3.3	18	1.7	1	2.7	68	2.2	1.7	2.7	24	2.3	1.5	3.4
	Infection bacterial (0738)	1	0.1	0	0.5	2	0.2	0	0.7	0	0	0	0.3	3	0.1	0	0.3	1	0.1	0	0.5

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 54 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
	Infection viral (0740)	194	18.5	16.2	21	185	17.6	15.4	20.1	185	17.5	15.3	20	564	17.9	16.6	19.3	205	19.4	17	21.9
	Moniliasis (0741)	7	0.7	0.3	1.4	12	1.1	0.6	2	3	0.3	0.1	0.8	22	0.7	0.4	1.1	5	0.5	0.2	1.1
	Otitis media (0750)	5	0.5	0.2	1.1	11	1	0.5	1.9	3	0.3	0.1	0.8	19	0.6	0.4	0.9	11	1	0.5	1.9
	Upper resp tract infection (0543)	47	4.5	3.3	5.9	38	3.6	2.6	4.9	49	4.6	3.5	6.1	134	4.3	3.6	5	42	4	2.9	5.3
Respiratory system (1100)	Asthma (1367)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Atelectasis (1197)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Bronchitis (0805)	21	2	1.2	3	30	2.9	1.9	4.1	21	2	1.2	3	72	2.3	1.8	2.9	14	1.3	0.7	2.2
	Bronchospasm (0511)	14	1.3	0.7	2.2	9	0.9	0.4	1.6	12	1.1	0.6	2	35	1.1	0.8	1.5	8	0.8	0.3	1.5
	Coughing (0513)	34	3.2	2.3	4.5	25	2.4	1.5	3.5	31	2.9	2	4.1	90	2.9	2.3	3.5	21	2	1.2	3
	Dyspnea (0514)	0	0	0	0.4	1	0.1	0	0.5	1	0.1	0	0.5	2	0.1	0	0.2	1	0.1	0	0.5
	Laryngitis (0521)	1	0.1	0	0.5	3	0.3	0.1	0.8	2	0.2	0	0.7	6	0.2	0.1	0.4	2	0.2	0	0.7
	Pharyngitis (0523)	75	7.2	5.7	8.9	100	9.5	7.8	11.5	82	7.8	6.2	9.6	257	8.2	7.2	9.2	85	8	6.5	9.8
	Pneumonia (0528)	14	1.3	0.7	2.2	25	2.4	1.5	3.5	21	2	1.2	3	60	1.9	1.5	2.4	20	1.9	1.2	2.9
	Respiratory disorder (0536)	0	0	0	0.4	7	0.7	0.3	1.4	1	0.1	0	0.5	8	0.3	0.1	0.5	2	0.2	0	0.7
	Rhinitis (0539)	9	0.9	0.4	1.6	15	1.4	0.8	2.3	13	1.2	0.7	2.1	37	1.2	0.8	1.6	14	1.3	0.7	2.2
	Sputum increased (0541)	3	0.3	0.1	0.8	9	0.9	0.4	1.6	2	0.2	0	0.7	14	0.4	0.2	0.7	3	0.3	0.1	0.8
Secondary term (2000)	Varicella (1516)	2	0.2	0	0.7	1	0.1	0	0.5	1	0.1	0	0.5	4	0.1	0	0.3	4	0.4	0.1	1
Skin and appendages (100)	Alopecia (0002)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Dermatitis (0007)	2	0.2	0	0.7	4	0.4	0.1	1	5	0.5	0.2	1.1	11	0.3	0.2	0.6	0	0	0	0.3
	Dermatitis fungal (0009)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Furunculosis (0016)	3	0.3	0.1	0.8	1	0.1	0	0.5	1	0.1	0	0.5	5	0.2	0.1	0.4	0	0	0	0.3

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 54 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
	Photosensitivity reaction (0022)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Pruritus (0024)	0	0	0	0.4	3	0.3	0.1	0.8	2	0.2	0	0.7	5	0.2	0.1	0.4	0	0	0	0.3
	Rash (0027)	1	0.1	0	0.5	1	0.1	0	0.5	0	0	0	0.3	2	0.1	0	0.2	0	0	0	0.3
	Rash erythematous (0028)	2	0.2	0	0.7	1	0.1	0	0.5	0	0	0	0.3	3	0.1	0	0.3	1	0.1	0	0.5
	Rash maculo-papular (0030)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	1	0.1	0	0.5
	Rash pustular (0032)	0	0	0	0.4	2	0.2	0	0.7	3	0.3	0.1	0.8	5	0.2	0.1	0.4	2	0.2	0	0.7
	Seborrhea (0033)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Skin disorder (0037)	6	0.6	0.2	1.2	8	0.8	0.3	1.5	10	0.9	0.5	1.7	24	0.8	0.5	1.1	10	0.9	0.5	1.7
	Sweat gland disorder (1166)	1	0.1	0	0.5	1	0.1	0	0.5	2	0.2	0	0.7	4	0.1	0	0.3	0	0	0	0.3
Urinary system (1300)	Dysuria (0601)	0	0	0	0.4	1	0.1	0	0.5	2	0.2	0	0.7	3	0.1	0	0.3	0	0	0	0.3
	Urinary tract infection (0628)	0	0	0	0.4	0	0	0	0.4	2	0.2	0	0.7	2	0.1	0	0.2	3	0.3	0.1	0.8
Vision (431)	Blepharitis (1007)	1	0.1	0	0.5	0	0	0	0.4	1	0.1	0	0.5	2	0.1	0	0.2	0	0	0	0.3
	Conjunctivitis (0238)	13	1.2	0.7	2.1	13	1.2	0.7	2.1	9	0.9	0.4	1.6	35	1.1	0.8	1.5	10	0.9	0.5	1.7
White cell and reticuloendothelial system (1220)	Lymphadenopathy cervical (0578)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	0	0	0	0.3

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 55: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		2	0.2	0	0.7	0	0	0	0.4	0	0	0	0.3	2	0.1	0	0.2	4	0.4	0.1	1
Application site (1820)	Injection site reaction (0058)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Fever (0725)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Pallor (0220)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Respiratory system (1100)	Bronchitis (0805)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3

Notes: D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 56: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		15	1.4	0.8	2.3	27	2.6	1.7	3.7	14	1.3	0.7	2.2	56	1.8	1.3	2.3	18	1.7	1	2.7
Application site (1820)	Dermatitis contact (0049)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Allergic reaction (0712)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Death, nos (0722)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	0	0	0	0.3
	Edema generalised (0400)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
	Fever (0725)	0	0	0	0.4	2	0.2	0	0.7	1	0.1	0	0.5	3	0.1	0	0.3	0	0	0	0.3
	Pallor (0220)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Central and peripheral nervous system (410)	Fever convulsions (1357)	1	0.1	0	0.5	0	0	0	0.4	1	0.1	0	0.5	2	0.1	0	0.2	0	0	0	0.3
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.3	0	0	0	0.1	1	0.1	0	0.5
Gastrointestinal system (600)	Abdominal pain (0268)	2	0.2	0	0.7	3	0.3	0.1	0.8	1	0.1	0	0.5	6	0.2	0.1	0.4	0	0	0	0.3
	Anorexia (0165)	1	0.1	0	0.5	0	0	0	0.4	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Constipation (0204)	0	0	0	0.4	1	0.1	0	0.5	1	0.1	0	0.5	2	0.1	0	0.2	0	0	0	0.3
	Gastroenteritis (0293)	3	0.3	0.1	0.8	5	0.5	0.2	1.1	1	0.1	0	0.5	9	0.3	0.1	0.5	4	0.4	0.1	1
	Gastrointestinal disorder nos (1262)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.5	1	0	0	0.2	1	0.1	0	0.5
Psychiatric (500)	Nervousness (0188)	1	0.1	0	0.5	1	0.1	0	0.5	1	0.1	0	0.5	3	0.1	0	0.3	0	0	0	0.3

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 56 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Resistance mechanism (1830)	Infection (0736)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	1	0.1	0	0.5
	Moniliasis (0741)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
Respiratory system (1100)	Asthma (1367)	0	0	0	0.4	1	0.1	0	0.5	0	0	0	0.3	1	0	0	0.2	0	0	0	0.3
	Bronchitis (0805)	2	0.2	0	0.7	4	0.4	0.1	1	0	0	0	0.3	6	0.2	0.1	0.4	0	0	0	0.3
	Pharyngitis (0523)	3	0.3	0.1	0.8	7	0.7	0.3	1.4	2	0.2	0	0.7	12	0.4	0.2	0.7	2	0.2	0	0.7
	Pneumonia (0528)	5	0.5	0.2	1.1	8	0.8	0.3	1.5	6	0.6	0.2	1.2	19	0.6	0.4	0.9	6	0.6	0.2	1.2

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 57: Percentage of subjects with gastrointestinal symptoms (unsolicited symptoms), from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)		**HRV_4.7 N = 538**				**HRV_5.2 N = 540**				**HRV_5.8 N = 540**				**Pooled HRV groups N = 1618**				**Placebo N = 537**			
				95% CI				**95% CI**				**95% CI**				**95% CI**				**95% CI**	
		s	**%**	**LL**	**UL**	**s**	**%**	**LL**	**UL**	**s**	**%**	**LL**	**UL**	**s**	**%**	**LL**	**UL**	**s**	**%**	**LL**	**UL**
Gastrointestinal system (600)	Any	68	12.6	10	15.7	69	12.8	10.1	15.9	55	10.2	7.8	13.1	192	11.9	10.3	13.5	69	12.8	10.1	16
	Related	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.7	0	0.0	0.0	0.2	0	0.0	0.0	0.7
	Grade 3	6	1.1	0.4	2.4	9	1.7	0.8	3.1	3	0.6	0.1	1.6	18	1.1	0.7	1.8	5	0.9	0.3	2.2

Notes: N = number of subjects having received at least one dose
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 58: Percentage of doses with gastrointestinal symptoms (unsolicited symptoms), from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)		HRV_4.7 D = 1048				HRV_5.2 D = 1049				HRV_5.8 D = 1055				Pooled HRV groups D = 3152				Placebo D = 1059			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Gastrointestinal system (600)	Any	80	7.6	6.1	9.4	81	7.7	6.2	9.5	68	6.4	5	8.1	229	7.3	6.4	8.2	75	7.1	5.6	8.8
	Related	0	0.0	0.0	0.4	0	0.0	0.0	0.4	0	0.0	0.0	0.3	0	0.0	0.0	0.1	0	0.0	0.0	0.3
	Grade 3	6	0.6	0.2	1.2	9	0.9	0.4	1.6	3	0.3	0.1	0.8	18	0.6	0.3	0.9	5	0.5	0.2	1.1

Notes: D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 59: Number and percentage of doses and of subjects who took at least one concomitant medication from Day 0 to Day 14 after vaccination by type (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

	Overall/dose											
	HRV_4.7 (N=1048)				HRV_5.2 (N=1049)				HRV_5.8 (N=1055)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL			LL	UL
Any medication	652	62.2	59.2	65.2	684	65.2	62.2	68.1	663	62.8	59.8	65.8
Any antipyretic	640	61.1	58.0	64.0	664	63.3	60.3	66.2	647	61.3	58.3	64.3
Prophylactic antipyretic	124	11.8	9.9	13.9	134	12.8	10.8	14.9	130	12.3	10.4	14.5
Any antibiotic	25	2.4	1.5	3.5	43	4.1	3.0	5.5	26	2.5	1.6	3.6

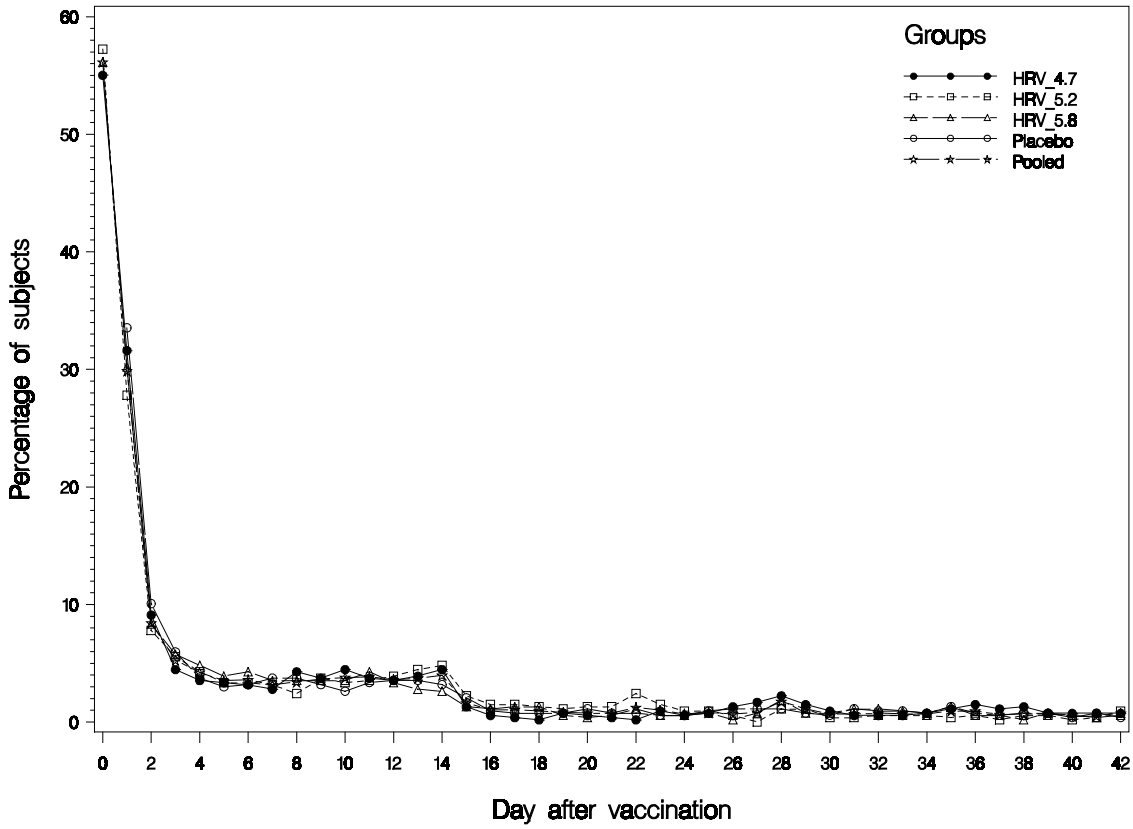
	Pooled HRV groups (N=3152)				Placebo (N=1059)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL
Any medication	1999	63.4	61.7	65.1	700	66.1	63.2	69.0
Any antipyretic	1951	61.9	60.2	63.6	682	64.4	61.4	67.3
Prophylactic antipyretic	388	12.3	11.2	13.5	130	12.3	10.4	14.4
Any antibiotic	94	3.0	2.4	3.6	30	2.8	1.9	4.0

	Overall/subject											
	HRV $10^{4.7}$ (N=538)				HRV $10^{5.2}$ (N=540)				HRV $10^{5.8}$ (N=540)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL			LL	UL
Any medication	428	79.6	75.9	82.9	446	82.6	79.1	85.7	430	79.6	76.0	82.9
Any antipyretic	425	79.0	75.3	82.4	438	81.1	77.6	84.3	422	78.1	74.4	81.6
Prophylactic antipyretic	98	18.2	15.0	21.7	111	20.6	17.2	24.2	100	18.5	15.3	22.1
Any antibiotic	25	4.6	3.0	6.8	41	7.6	5.5	10.2	25	4.6	3.0	6.8

	Pooled HRV groups (N=1618)				Placebo (N=537)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL
Any medication	1304	80.6	78.6	82.5	446	83.1	79.6	86.1
Any antipyretic	1285	79.4	77.4	81.4	438	81.6	78.0	84.8
Prophylactic antipyretic	309	19.1	17.2	21.1	102	19.0	15.8	22.6
Any antibiotic	91	5.6	4.6	6.9	28	5.2	3.5	7.4

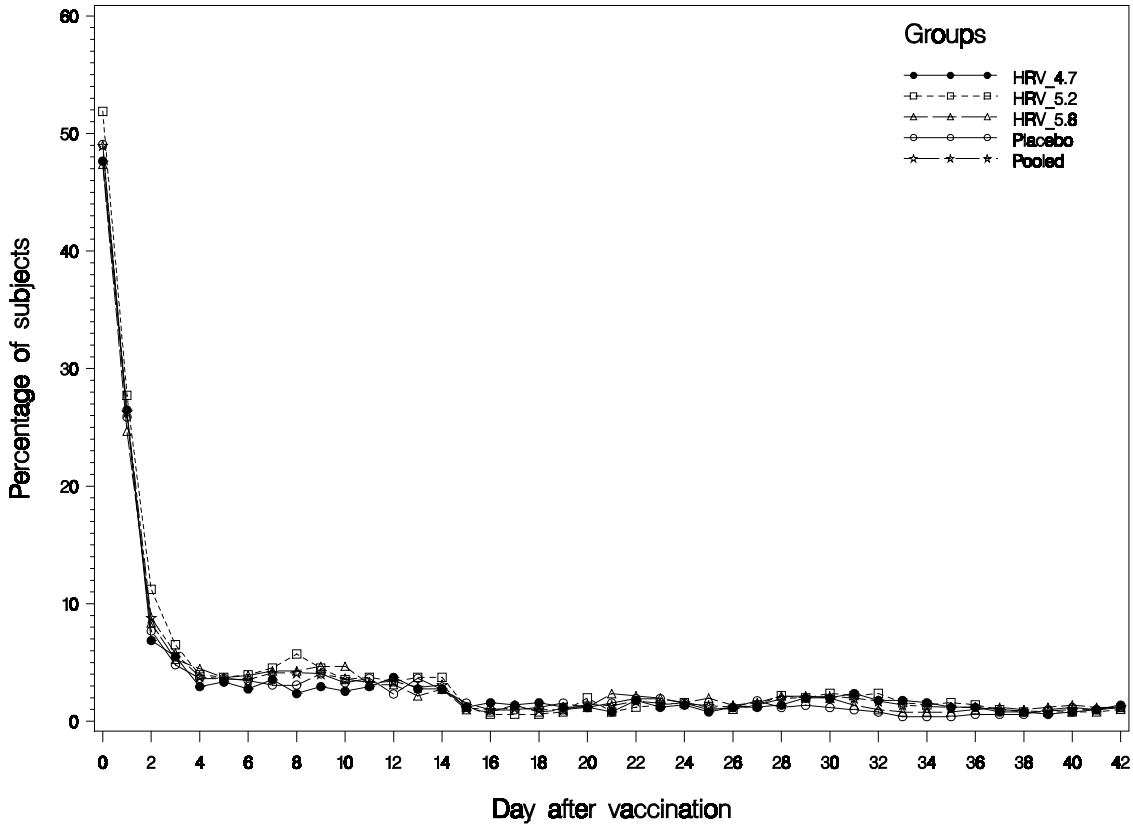
Notes: For overall/dose:
N = total number of doses administered
n/% = number/percentage of doses with at least one specified concomitant medication, from Day 0 to Day 14.
For Overall/subject: N= total number of subjects having received at least one dose
n/% = total number/percentage of subject having who started taking the specified concomitant medication at least once after the considered dose, from Day 0 to Day 14
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 60: Percentage of subjects who took antipyretics after Dose 1, by day from Day 0 to Day 42 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



pooled = pooled HRV groups

Supplement 61: Percentage of subjects who took antipyretics after Dose 2, by day from Day 0 to Day 42 (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)



pooled = pooled HRV groups

Supplement 62: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	194	187	96.4	92.7	98.5
	HRV_5.2	196	191	97.4	94.1	99.2
	HRV_5.8	194	192	99.0	96.3	99.9
	Pooled HRV groups	584	570	97.6	96.0	98.7
	Placebo	194	191	98.5	95.5	99.7
Dose 2	**HRV_4.7**	187	169	90.4	85.2	94.2
	HRV_5.2	183	172	94.0	89.5	97.0
	HRV_5.8	192	181	94.3	90.0	97.1
	Pooled HRV groups	562	522	92.9	90.4	94.9
	Placebo	191	171	89.5	84.3	93.5
Overall/dose	**HRV_4.7**	381	356	93.4	90.5	95.7
	HRV_5.2	379	363	95.8	93.2	97.6
	HRV_5.8	386	373	96.6	94.3	98.2
	Pooled HRV groups	1146	1092	95.3	93.9	96.4
	Placebo	385	362	94.0	91.2	96.2
Overall/subject	**HRV_4.7**	194	191	98.5	95.5	99.7
	HRV_5.2	196	193	98.5	95.6	99.7
	HRV_5.8	194	194	100.0	98.1	100.0
	Pooled HRV groups	584	578	99.0	97.8	99.6
	Placebo	194	192	99.0	96.3	99.9

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 63: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	101	92	91.1	83.8	95.8
	HRV_5.2	101	94	93.1	86.2	97.2
	HRV_5.8	102	95	93.1	86.4	97.2
	Pooled HRV groups	304	281	92.4	88.9	95.1
	Placebo	101	95	94.1	87.5	97.8
Dose 2	**HRV_4.7**	88	73	83.0	73.4	90.1
	HRV_5.2	95	83	87.4	79.0	93.3
	HRV_5.8	90	81	90.0	81.9	95.3
	Pooled HRV groups	273	237	86.8	82.2	90.6
	Placebo	97	84	86.6	78.2	92.7
Overall/dose	**HRV_4.7**	189	165	87.3	81.7	91.7
	HRV_5.2	196	177	90.3	85.3	94.1
	HRV_5.8	192	176	91.7	86.8	95.2
	Pooled HRV groups	577	518	89.8	87.0	92.1
	Placebo	198	179	90.4	85.4	94.1
Overall/subject	**HRV_4.7**	101	94	93.1	86.2	97.2
	HRV_5.2	101	96	95.0	88.8	98.4
	HRV_5.8	102	97	95.1	88.9	98.4
	Pooled HRV groups	304	287	94.4	91.2	96.7
	Placebo	101	98	97.0	91.6	99.4

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 64: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	243	211	86.8	81.9	90.8
	HRV_5.2	243	206	84.8	79.6	89.0
	HRV_5.8	244	208	85.2	80.2	89.4
	Pooled HRV groups	730	625	85.6	82.9	88.1
	Placebo	242	214	88.4	83.7	92.2
Dose 2	**HRV_4.7**	235	195	83.0	77.6	87.6
	HRV_5.2	231	194	84.0	78.6	88.5
	HRV_5.8	233	189	81.1	75.5	85.9
	Pooled HRV groups	699	578	82.7	79.7	85.4
	Placebo	234	202	86.3	81.2	90.5
Overall/dose	**HRV_4.7**	478	406	84.9	81.4	88.0
	HRV_5.2	474	400	84.4	80.8	87.5
	HRV_5.8	477	397	83.2	79.6	86.5
	Pooled HRV groups	1429	1203	84.2	82.2	86.0
	Placebo	476	416	87.4	84.1	90.2
Overall/subject	**HRV_4.7**	243	229	94.2	90.5	96.8
	HRV_5.2	243	227	93.4	89.5	96.2
	HRV_5.8	244	224	91.8	87.6	94.9
	Pooled HRV groups	730	680	93.2	91.1	94.9
	Placebo	242	231	95.5	92.0	97.7

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 65: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	194	29	14.9	10.2	20.8
	HRV_5.2	196	39	19.9	14.5	26.2
	HRV_5.8	194	45	23.2	17.5	29.8
	Pooled HRV groups	584	113	19.3	16.2	22.8
	Placebo	194	43	22.2	16.5	28.7
Dose 2	**HRV_4.7**	187	38	20.3	14.8	26.8
	HRV_5.2	183	40	21.9	16.1	28.6
	HRV_5.8	192	37	19.3	13.9	25.6
	Pooled HRV groups	562	115	20.5	17.2	24.0
	Placebo	191	34	17.8	12.7	24.0
Overall/dose	**HRV_4.7**	381	67	17.6	13.9	21.8
	HRV_5.2	379	79	20.8	16.9	25.3
	HRV_5.8	386	82	21.2	17.3	25.7
	Pooled HRV groups	1146	228	19.9	17.6	22.3
	Placebo	385	77	20.0	16.1	24.3
Overall/subject	**HRV_4.7**	194	60	30.9	24.5	37.9
	HRV_5.2	196	72	36.7	30.0	43.9
	HRV_5.8	194	70	36.1	29.3	43.3
	Pooled HRV groups	584	202	34.6	30.7	38.6
	Placebo	194	65	33.5	26.9	40.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 66: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	101	16	15.8	9.3	24.4
	HRV_5.2	101	13	12.9	7.0	21.0
	HRV_5.8	102	13	12.7	7.0	20.8
	Pooled HRV groups	304	42	13.8	10.1	18.2
	Placebo	101	9	8.9	4.2	16.2
Dose 2	**HRV_4.7**	88	5	5.7	1.9	12.8
	HRV_5.2	95	15	15.8	9.1	24.7
	HRV_5.8	90	12	13.3	7.1	22.1
	Pooled HRV groups	273	32	11.7	8.2	16.1
	Placebo	97	12	12.4	6.6	20.6
Overall/dose	**HRV_4.7**	189	21	11.1	7.0	16.5
	HRV_5.2	196	28	14.3	9.7	20.0
	HRV_5.8	192	25	13.0	8.6	18.6
	Pooled HRV groups	577	74	12.8	10.2	15.8
	Placebo	198	21	10.6	6.7	15.8
Overall/subject	**HRV_4.7**	101	19	18.8	11.7	27.8
	HRV_5.2	101	27	26.7	18.4	36.5
	HRV_5.8	102	20	19.6	12.4	28.6
	Pooled HRV groups	304	66	21.7	17.2	26.8
	Placebo	101	19	18.8	11.7	27.8

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 67: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	243	69	28.4	22.8	34.5
	HRV_5.2	243	76	31.3	25.5	37.5
	HRV_5.8	244	82	33.6	27.7	39.9
	Pooled HRV groups	730	227	31.1	27.8	34.6
	Placebo	242	77	31.8	26.0	38.1
Dose 2	**HRV_4.7**	235	62	26.4	20.9	32.5
	HRV_5.2	231	56	24.2	18.9	30.3
	HRV_5.8	233	65	27.9	22.2	34.1
	Pooled HRV groups	699	183	26.2	23.0	29.6
	Placebo	234	58	24.8	19.4	30.8
Overall/dose	**HRV_4.7**	478	131	27.4	23.5	31.6
	HRV_5.2	474	132	27.8	23.9	32.1
	HRV_5.8	477	147	30.8	26.7	35.2
	Pooled HRV groups	1429	410	28.7	26.4	31.1
	Placebo	476	135	28.4	24.4	32.6
Overall/subject	**HRV_4.7**	243	101	41.6	35.3	48.0
	HRV_5.2	243	105	43.2	36.9	49.7
	HRV_5.8	244	106	43.4	37.1	49.9
	Pooled HRV groups	730	312	42.7	39.1	46.4
	Placebo	242	106	43.8	37.5	50.3

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N = number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 68: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	194	184	94.8	90.7	97.5
	HRV_5.2	196	185	94.4	90.2	97.2
	HRV_5.8	194	181	93.3	88.8	96.4
	Pooled HRV groups	584	550	94.2	92.0	95.9
	Placebo	194	183	94.3	90.1	97.1
Dose 2	**HRV_4.7**	187	150	80.2	73.8	85.7
	HRV_5.2	183	152	83.1	76.8	88.2
	HRV_5.8	192	164	85.4	79.6	90.1
	Pooled HRV groups	562	466	82.9	79.5	85.9
	Placebo	191	142	74.3	67.5	80.4
Overall/dose	**HRV_4.7**	381	334	87.7	83.9	90.8
	HRV_5.2	379	337	88.9	85.3	91.9
	HRV_5.8	386	345	89.4	85.9	92.3
	Pooled HRV groups	1146	1016	88.7	86.7	90.4
	Placebo	385	325	84.4	80.4	87.9
Overall/Subject	**HRV_4.7**	194	190	97.9	94.8	99.4
	HRV_5.2	196	192	98.0	94.9	99.4
	HRV_5.8	194	192	99.0	96.3	99.9
	Pooled HRV groups	584	574	98.3	96.9	99.2
	Placebo	194	184	94.8	90.7	97.5

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 69: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	101	90	89.1	81.3	94.4
	HRV_5.2	101	93	92.1	85.0	96.5
	HRV_5.8	102	90	88.2	80.4	93.8
	Pooled HRV groups	304	273	89.8	85.8	93.0
	Placebo	101	92	91.1	83.8	95.8
Dose 2	**HRV_4.7**	88	68	77.3	67.1	85.5
	HRV_5.2	95	80	84.2	75.3	90.9
	HRV_5.8	90	76	84.4	75.3	91.2
	Pooled HRV groups	273	224	82.1	77.0	86.4
	Placebo	97	81	83.5	74.6	90.3
Overall/dose	**HRV_4.7**	189	158	83.6	77.5	88.6
	HRV_5.2	196	173	88.3	82.9	92.4
	HRV_5.8	192	166	86.5	80.8	91.0
	Pooled HRV groups	577	497	86.1	83.0	88.9
	Placebo	198	173	87.4	81.9	91.7
Overall/subject	**HRV_4.7**	101	94	93.1	86.2	97.2
	HRV_5.2	101	95	94.1	87.5	97.8
	HRV_5.8	102	95	93.1	86.4	97.2
	Pooled HRV groups	304	284	93.4	90.0	95.9
	Placebo	101	96	95.0	88.8	98.4

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 70: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	243	1	0.4	0.0	2.3
	HRV_5.2	243	0	0.0	0.0	1.5
	HRV_5.8	244	0	0.0	0.0	1.5
	Pooled HRV groups	730	1	0.1	0.0	0.8
	Placebo	242	1	0.4	0.0	2.3
Dose 2	**HRV_4.7**	235	0	0.0	0.0	1.6
	HRV_5.2	231	2	0.9	0.1	3.1
	HRV_5.8	233	0	0.0	0.0	1.6
	Pooled HRV groups	699	2	0.3	0.0	1.0
	Placebo	234	0	0.0	0.0	1.6
Overall/dose	**HRV_4.7**	478	1	0.2	0.0	1.2
	HRV_5.2	474	2	0.4	0.1	1.5
	HRV_5.8	477	0	0.0	0.0	0.8
	Pooled HRV groups	1429	3	0.2	0.0	0.6
	Placebo	476	1	0.2	0.0	1.2
Overall/subject	**HRV_4.7**	243	1	0.4	0.0	2.3
	HRV_5.2	243	2	0.8	0.1	2.9
	HRV_5.8	244	0	0.0	0.0	1.5
	Pooled HRV groups	730	3	0.4	0.1	1.2
	Placebo	242	1	0.4	0.0	2.3

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/%= number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71: Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		1											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		194				196				194			
COUGH	Total	125	64.4	57.3	71.2	131	66.8	59.8	73.4	119	61.3	54.1	68.2
	Grade 2*3	54	27.8	21.7	34.7	42	21.4	15.9	27.8	56	28.9	22.6	35.8
	Grade 3	7	3.6	1.5	7.3	9	4.6	2.1	8.5	10	5.2	2.5	9.3
	Related	66	34.0	27.4	41.2	62	31.6	25.2	38.6	50	25.8	19.8	32.5
DIARRHEA	Total	22	11.3	7.2	16.7	24	12.2	8.0	17.7	29	14.9	10.2	20.8
	Grade 2*3	12	6.2	3.2	10.6	15	7.7	4.3	12.3	15	7.7	4.4	12.4
	Grade 3	5	2.6	0.8	5.9	7	3.6	1.4	7.2	6	3.1	1.1	6.6
	Related	11	5.7	2.9	9.9	14	7.1	4.0	11.7	20	10.3	6.4	15.5
IRRITABILITY	Total	164	84.5	78.7	89.3	160	81.6	75.5	86.8	167	86.1	80.4	90.6
	Grade 2*3	117	60.3	53.1	67.2	93	47.4	40.3	54.7	121	62.4	55.1	69.2
	Grade 3	17	8.8	5.2	13.7	21	10.7	6.8	15.9	23	11.9	7.7	17.3
	Related	156	80.4	74.1	85.8	155	79.1	72.7	84.6	161	83.0	76.9	88.0
LOSS OF APPETITE	Total	54	27.8	21.7	34.7	57	29.1	22.8	36.0	58	29.9	23.5	36.9
	Grade 2*3	24	12.4	8.1	17.8	18	9.2	5.5	14.1	24	12.4	8.1	17.8
	Grade 3	4	2.1	0.6	5.2	1	0.5	0.0	2.8	1	0.5	0.0	2.8
	Related	39	20.1	14.7	26.4	42	21.4	15.9	27.8	44	22.7	17.0	29.2
FEVER	Total	148	76.3	69.7	82.1	144	73.5	66.7	79.5	140	72.2	65.3	78.3
	Grade 2*3	75	38.7	31.8	45.9	66	33.7	27.1	40.8	74	38.1	31.3	45.4
	Grade 3	2	1.0	0.1	3.7	3	1.5	0.3	4.4	4	2.1	0.6	5.2
	Related	144	74.2	67.5	80.2	137	69.9	63.0	76.2	132	68.0	61.0	74.5
VOMITING	Total	46	23.7	17.9	30.3	53	27.0	21.0	33.8	47	24.2	18.4	30.9
	Grade 2*3	15	7.7	4.4	12.4	29	14.8	10.1	20.6	20	10.3	6.4	15.5
	Grade 3	5	2.6	0.8	5.9	9	4.6	2.1	8.5	10	5.2	2.5	9.3
	Related	31	16.0	11.1	21.9	30	15.3	10.6	21.1	27	13.9	9.4	19.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		**1**							
Group		**Pooled HRV groups**				**Placebo**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
N		584				194			
COUGH	**Total**	375	64.2	60.2	68.1	133	68.6	61.5	75.0
	Grade 2*3	152	26.0	22.5	29.8	61	31.4	25.0	38.5
	Grade 3	26	4.5	2.9	6.5	6	3.1	1.1	6.6
	Related	178	30.5	26.8	34.4	61	31.4	25.0	38.5
DIARRHEA	**Total**	75	12.8	10.2	15.8	28	14.4	9.8	20.2
	Grade 2*3	42	7.2	5.2	9.6	16	8.2	4.8	13.0
	Grade 3	18	3.1	1.8	4.8	6	3.1	1.1	6.6
	Related	45	7.7	5.7	10.2	13	6.7	3.6	11.2
IRRITABILITY	**Total**	491	84.1	80.9	87.0	170	87.6	82.2	91.9
	Grade 2*3	331	56.7	52.5	60.7	115	59.3	52.0	66.3
	Grade 3	61	10.4	8.1	13.2	27	13.9	9.4	19.6
	Related	472	80.8	77.4	83.9	165	85.1	79.2	89.8
LOSS OF APPETITE	**Total**	169	28.9	25.3	32.8	66	34.0	27.4	41.2
	Grade 2*3	66	11.3	8.8	14.2	27	13.9	9.4	19.6
	Grade 3	6	1.0	0.4	2.2	2	1.0	0.1	3.7
	Related	125	21.4	18.1	25.0	54	27.8	21.7	34.7
FEVER	**Total**	432	74.0	70.2	77.5	143	73.7	66.9	79.8
	Grade 2*3	215	36.8	32.9	40.9	71	36.6	29.8	43.8
	Grade 3	9	1.5	0.7	2.9	6	3.1	1.1	6.6
	Related	413	70.7	66.8	74.4	137	70.6	63.7	76.9
VOMITING	**Total**	146	25.0	21.5	28.7	49	25.3	19.3	32.0
	Grade 2*3	64	11.0	8.5	13.8	21	10.8	6.8	16.1
	Grade 3	24	4.1	2.7	6.1	5	2.6	0.8	5.9
	Related	88	15.1	12.3	18.2	37	19.1	13.8	25.3

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		2											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		187				183				192			
COUGH	Total	125	66.8	59.6	73.5	133	72.7	65.6	79.0	129	67.2	60.1	73.8
	Grade 2*3	67	35.8	29.0	43.2	60	32.8	26.0	40.1	58	30.2	23.8	37.2
	Grade 3	15	8.0	4.6	12.9	16	8.7	5.1	13.8	13	6.8	3.7	11.3
	Related	61	32.6	26.0	39.8	66	36.1	29.1	43.5	70	36.5	29.6	43.7
DIARRHEA	Total	31	16.6	11.6	22.7	28	15.3	10.4	21.3	28	14.6	9.9	20.4
	Grade 2*3	23	12.3	8.0	17.9	21	11.5	7.2	17.0	15	7.8	4.4	12.6
	Grade 3	5	2.7	0.9	6.1	11	6.0	3.0	10.5	6	3.1	1.2	6.7
	Related	17	9.1	5.4	14.2	20	10.9	6.8	16.4	13	6.8	3.7	11.3
IRRITABILITY	Total	120	64.2	56.8	71.0	121	66.1	58.8	72.9	123	64.1	56.8	70.8
	Grade 2*3	64	34.2	27.5	41.5	61	33.3	26.6	40.7	65	33.9	27.2	41.0
	Grade 3	16	8.6	5.0	13.5	12	6.6	3.4	11.2	6	3.1	1.2	6.7
	Related	112	59.9	52.5	67.0	113	61.7	54.3	68.8	117	60.9	53.7	67.9
LOSS OF APPETITE	Total	56	29.9	23.5	37.1	45	24.6	18.5	31.5	47	24.5	18.6	31.2
	Grade 2*3	27	14.4	9.7	20.3	24	13.1	8.6	18.9	18	9.4	5.7	14.4
	Grade 3	3	1.6	0.3	4.6	6	3.3	1.2	7.0	3	1.6	0.3	4.5
	Related	38	20.3	14.8	26.8	34	18.6	13.2	25.0	29	15.1	10.4	21.0
FEVER	Total	113	60.4	53.0	67.5	89	48.6	41.2	56.1	116	60.4	53.1	67.4
	Grade 2*3	58	31.0	24.5	38.2	46	25.1	19.0	32.1	58	30.2	23.8	37.2
	Grade 3	7	3.7	1.5	7.6	6	3.3	1.2	7.0	7	3.6	1.5	7.4
	Related	99	52.9	45.5	60.3	79	43.2	35.9	50.7	106	55.2	47.9	62.4
VOMITING	Total	33	17.6	12.5	23.9	36	19.7	14.2	26.2	34	17.7	12.6	23.9
	Grade 2*3	14	7.5	4.2	12.2	22	12.0	7.7	17.6	17	8.9	5.2	13.8
	Grade 3	9	4.8	2.2	8.9	10	5.5	2.7	9.8	9	4.7	2.2	8.7
	Related	23	12.3	8.0	17.9	20	10.9	6.8	16.4	20	10.4	6.5	15.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		2							
		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		562				191			
COUGH	Total	387	68.9	64.9	72.7	138	72.3	65.3	78.5
	Grade 2*3	185	32.9	29.0	37.0	67	35.1	28.3	42.3
	Grade 3	44	7.8	5.7	10.4	13	6.8	3.7	11.4
	Related	197	35.1	31.1	39.2	60	31.4	24.9	38.5
DIARRHEA	Total	87	15.5	12.6	18.7	28	14.7	10.0	20.5
	Grade 2*3	59	10.5	8.1	13.3	22	11.5	7.4	16.9
	Grade 3	22	3.9	2.5	5.9	10	5.2	2.5	9.4
	Related	50	8.9	6.7	11.6	11	5.8	2.9	10.1
IRRITABILITY	Total	364	64.8	60.7	68.7	108	56.5	49.2	63.7
	Grade 2*3	190	33.8	29.9	37.9	59	30.9	24.4	38.0
	Grade 3	34	6.0	4.2	8.4	8	4.2	1.8	8.1
	Related	342	60.9	56.7	64.9	100	52.4	45.0	59.6
LOSS OF APPETITE	Total	148	26.3	22.7	30.2	46	24.1	18.2	30.8
	Grade 2*3	69	12.3	9.7	15.3	21	11.0	6.9	16.3
	Grade 3	12	2.1	1.1	3.7	1	0.5	0.0	2.9
	Related	101	18.0	14.9	21.4	32	16.8	11.8	22.8
FEVER	Total	318	56.6	52.4	60.7	101	52.9	45.5	60.1
	Grade 2*3	162	28.8	25.1	32.8	44	23.0	17.3	29.7
	Grade 3	20	3.6	2.2	5.4	7	3.7	1.5	7.4
	Related	284	50.5	46.3	54.7	82	42.9	35.8	50.3
VOMITING	Total	103	18.3	15.2	21.8	26	13.6	9.1	19.3
	Grade 2*3	53	9.4	7.1	12.2	12	6.3	3.3	10.7
	Grade 3	28	5.0	3.3	7.1	6	3.1	1.2	6.7
	Related	63	11.2	8.7	14.1	16	8.4	4.9	13.2

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/Dose											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		381				379				386			
COUGH	Total	250	65.6	60.6	70.4	264	69.7	64.8	74.2	248	64.2	59.2	69.0
	Grade 2*3	121	31.8	27.1	36.7	102	26.9	22.5	31.7	114	29.5	25.0	34.4
	Grade 3	22	5.8	3.7	8.6	25	6.6	4.3	9.6	23	6.0	3.8	8.8
	Related	127	33.3	28.6	38.3	128	33.8	29.0	38.8	120	31.1	26.5	36.0
DIARRHEA	Total	53	13.9	10.6	17.8	52	13.7	10.4	17.6	57	14.8	11.4	18.7
	Grade 2*3	35	9.2	6.5	12.5	36	9.5	6.7	12.9	30	7.8	5.3	10.9
	Grade 3	10	2.6	1.3	4.8	18	4.7	2.8	7.4	12	3.1	1.6	5.4
	Related	28	7.3	4.9	10.4	34	9.0	6.3	12.3	33	8.5	6.0	11.8
IRRITABILITY	Total	284	74.5	69.9	78.8	281	74.1	69.4	78.5	290	75.1	70.5	79.4
	Grade 2*3	181	47.5	42.4	52.7	154	40.6	35.6	45.8	186	48.2	43.1	53.3
	Grade 3	33	8.7	6.0	11.9	33	8.7	6.1	12.0	29	7.5	5.1	10.6
	Related	268	70.3	65.5	74.9	268	70.7	65.8	75.2	278	72.0	67.3	76.4
LOSS OF APPETITE	Total	110	28.9	24.4	33.7	102	26.9	22.5	31.7	105	27.2	22.8	31.9
	Grade 2*3	51	13.4	10.1	17.2	42	11.1	8.1	14.7	42	10.9	8.0	14.4
	Grade 3	7	1.8	0.7	3.7	7	1.8	0.7	3.8	4	1.0	0.3	2.6
	Related	77	20.2	16.3	24.6	76	20.1	16.1	24.4	73	18.9	15.1	23.2
FEVER	Total	261	68.5	63.6	73.1	233	61.5	56.4	66.4	256	66.3	61.4	71.0
	Grade 2*3	133	34.9	30.1	39.9	112	29.6	25.0	34.4	132	34.2	29.5	39.2
	Grade 3	9	2.4	1.1	4.4	9	2.4	1.1	4.5	11	2.8	1.4	5.0
	Related	243	63.8	58.7	68.6	216	57.0	51.8	62.0	238	61.7	56.6	66.5
VOMITING	Total	79	20.7	16.8	25.2	89	23.5	19.3	28.1	81	21.0	17.0	25.4
	Grade 2*3	29	7.6	5.2	10.7	51	13.5	10.2	17.3	37	9.6	6.8	13.0
	Grade 3	14	3.7	2.0	6.1	19	5.0	3.0	7.7	19	4.9	3.0	7.6
	Related	54	14.2	10.8	18.1	50	13.2	10.0	17.0	47	12.2	9.1	15.9

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/Dose							
		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		1146				385			
COUGH	**Total**	762	66.5	63.7	69.2	271	70.4	65.6	74.9
	Grade 2*3	337	29.4	26.8	32.1	128	33.2	28.6	38.2
	Grade 3	70	6.1	4.8	7.7	19	4.9	3.0	7.6
	Related	375	32.7	30.0	35.5	121	31.4	26.8	36.3
DIARRHEA	**Total**	162	14.1	12.2	16.3	56	14.5	11.2	18.5
	Grade 2*3	101	8.8	7.2	10.6	38	9.9	7.1	13.3
	Grade 3	40	3.5	2.5	4.7	16	4.2	2.4	6.7
	Related	95	8.3	6.8	10.0	24	6.2	4.0	9.1
IRRITABILITY	**Total**	855	74.6	72.0	77.1	278	72.2	67.4	76.6
	Grade 2*3	521	45.5	42.6	48.4	174	45.2	40.1	50.3
	Grade 3	95	8.3	6.8	10.0	35	9.1	6.4	12.4
	Related	814	71.0	68.3	73.6	265	68.8	63.9	73.4
LOSS OF APPETITE	**Total**	317	27.7	25.1	30.4	112	29.1	24.6	33.9
	Grade 2*3	135	11.8	10.0	13.8	48	12.5	9.3	16.2
	Grade 3	18	1.6	0.9	2.5	3	0.8	0.2	2.3
	Related	226	19.7	17.5	22.1	86	22.3	18.3	26.8
FEVER	**Total**	750	65.4	62.6	68.2	244	63.4	58.3	68.2
	Grade 2*3	377	32.9	30.2	35.7	115	29.9	25.3	34.7
	Grade 3	29	2.5	1.7	3.6	13	3.4	1.8	5.7
	Related	697	60.8	57.9	63.7	219	56.9	51.8	61.9
VOMITING	**Total**	249	21.7	19.4	24.2	75	19.5	15.6	23.8
	Grade 2*3	117	10.2	8.5	12.1	33	8.6	6.0	11.8
	Grade 3	52	4.5	3.4	5.9	11	2.9	1.4	5.1
	Related	151	13.2	11.3	15.3	53	13.8	10.5	17.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/Subject											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		194				196				194			
COUGH	Total	158	81.4	75.2	86.7	167	85.2	79.4	89.9	161	83.0	76.9	88.0
	Grade 2*3	90	46.4	39.2	53.7	87	44.4	37.3	51.6	91	46.9	39.7	54.2
	Grade 3	21	10.8	6.8	16.1	24	12.2	8.0	17.7	21	10.8	6.8	16.1
	Related	97	50.0	42.8	57.2	105	53.6	46.3	60.7	100	51.5	44.3	58.8
DIARRHEA	Total	50	25.8	19.8	32.5	45	23.0	17.3	29.5	49	25.3	19.3	32.0
	Grade 2*3	33	17.0	12.0	23.1	34	17.3	12.3	23.4	28	14.4	9.8	20.2
	Grade 3	10	5.2	2.5	9.3	18	9.2	5.5	14.1	11	5.7	2.9	9.9
	Related	28	14.4	9.8	20.2	32	16.3	11.4	22.3	29	14.9	10.2	20.8
IRRITABILITY	Total	174	89.7	84.5	93.6	177	90.3	85.3	94.1	181	93.3	88.8	96.4
	Grade 2*3	134	69.1	62.1	75.5	116	59.2	52.0	66.1	136	70.1	63.1	76.5
	Grade 3	28	14.4	9.8	20.2	30	15.3	10.6	21.1	25	12.9	8.5	18.4
	Related	167	86.1	80.4	90.6	171	87.2	81.7	91.6	178	91.8	87.0	95.2
LOSS OF APPETITE	Total	88	45.4	38.2	52.6	78	39.8	32.9	47.0	82	42.3	35.2	49.6
	Grade 2*3	45	23.2	17.5	29.8	37	18.9	13.7	25.1	37	19.1	13.8	25.3
	Grade 3	7	3.6	1.5	7.3	6	3.1	1.1	6.5	4	2.1	0.6	5.2
	Related	65	33.5	26.9	40.6	62	31.6	25.2	38.6	60	30.9	24.5	37.9
FEVER	Total	171	88.1	82.7	92.3	161	82.1	76.1	87.2	163	84.0	78.1	88.9
	Grade 2*3	111	57.2	49.9	64.3	95	48.5	41.3	55.7	106	54.6	47.4	61.8
	Grade 3	9	4.6	2.1	8.6	9	4.6	2.1	8.5	11	5.7	2.9	9.9
	Related	166	85.6	79.8	90.2	151	77.0	70.5	82.7	157	80.9	74.7	86.2
VOMITING	Total	65	33.5	26.9	40.6	71	36.2	29.5	43.4	66	34.0	27.4	41.2
	Grade 2*3	26	13.4	8.9	19.0	43	21.9	16.4	28.4	35	18.0	12.9	24.2
	Grade 3	13	6.7	3.6	11.2	17	8.7	5.1	13.5	18	9.3	5.6	14.3
	Related	47	24.2	18.4	30.9	43	21.9	16.4	28.4	41	21.1	15.6	27.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 71 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/Subject							
		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		584				194			
COUGH	Total	486	83.2	79.9	86.2	171	88.1	82.7	92.3
	Grade 2*3	268	45.9	41.8	50.0	106	54.6	47.4	61.8
	Grade 3	66	11.3	8.8	14.2	19	9.8	6.0	14.9
	Related	302	51.7	47.6	55.8	97	50.0	42.8	57.2
DIARRHEA	Total	144	24.7	21.2	28.4	53	27.3	21.2	34.2
	Grade 2*3	95	16.3	13.4	19.5	37	19.1	13.8	25.3
	Grade 3	39	6.7	4.8	9.0	15	7.7	4.4	12.4
	Related	89	15.2	12.4	18.4	24	12.4	8.1	17.8
IRRITABILITY	Total	532	91.1	88.5	93.3	176	90.7	85.7	94.4
	Grade 2*3	386	66.1	62.1	69.9	133	68.6	61.5	75.0
	Grade 3	83	14.2	11.5	17.3	33	17.0	12.0	23.1
	Related	516	88.4	85.5	90.8	173	89.2	83.9	93.2
LOSS OF APPETITE	Total	248	42.5	38.4	46.6	88	45.4	38.2	52.6
	Grade 2*3	119	20.4	17.2	23.9	42	21.6	16.1	28.1
	Grade 3	17	2.9	1.7	4.6	3	1.5	0.3	4.5
	Related	187	32.0	28.3	36.0	71	36.6	29.8	43.8
FEVER	Total	495	84.8	81.6	87.6	164	84.5	78.7	89.3
	Grade 2*3	312	53.4	49.3	57.5	93	47.9	40.7	55.2
	Grade 3	29	5.0	3.4	7.1	12	6.2	3.2	10.6
	Related	474	81.2	77.8	84.3	155	79.9	73.6	85.3
VOMITING	Total	202	34.6	30.7	38.6	65	33.5	26.9	40.6
	Grade 2*3	104	17.8	14.8	21.2	31	16.0	11.1	21.9
	Grade 3	48	8.2	6.1	10.7	10	5.2	2.5	9.3
	Related	131	22.4	19.1	26.0	49	25.3	19.3	32.0

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72: Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		1											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		101				101				102			
COUGH	Total	54	53.5	43.3	63.5	50	49.5	39.4	59.6	50	49.0	39.0	59.1
	Grade 2*3	13	12.9	7.0	21.0	14	13.9	7.8	22.2	9	8.8	4.1	16.1
	Grade 3	4	4.0	1.1	9.8	1	1.0	0.0	5.4	2	2.0	0.2	6.9
	Related	43	42.6	32.8	52.8	40	39.6	30.0	49.8	41	40.2	30.6	50.4
DIARRHEA	Total	8	7.9	3.5	15.0	7	6.9	2.8	13.8	12	11.8	6.2	19.6
	Grade 2*3	5	5.0	1.6	11.2	6	5.9	2.2	12.5	10	9.8	4.8	17.3
	Grade 3	2	2.0	0.2	7.0	3	3.0	0.6	8.4	2	2.0	0.2	6.9
	Related	5	5.0	1.6	11.2	6	5.9	2.2	12.5	9	8.8	4.1	16.1
IRRITABILITY	Total	83	82.2	73.3	89.1	77	76.2	66.7	84.1	86	84.3	75.8	90.8
	Grade 2*3	27	26.7	18.4	36.5	37	36.6	27.3	46.8	36	35.3	26.1	45.4
	Grade 3	5	5.0	1.6	11.2	5	5.0	1.6	11.2	4	3.9	1.1	9.7
	Related	79	78.2	68.9	85.8	72	71.3	61.4	79.9	80	78.4	69.2	86.0
LOSS OF APPETITE	Total	41	40.6	30.9	50.8	44	43.6	33.7	53.8	38	37.3	27.9	47.4
	Grade 2*3	8	7.9	3.5	15.0	7	6.9	2.8	13.8	11	10.8	5.5	18.5
	Grade 3	0	0.0	0.0	3.6	2	2.0	0.2	7.0	0	0.0	0.0	3.6
	Related	35	34.7	25.5	44.8	36	35.6	26.4	45.8	34	33.3	24.3	43.4
FEVER	Total	64	63.4	53.2	72.7	59	58.4	48.2	68.1	66	64.7	54.6	73.9
	Grade 2*3	28	27.7	19.3	37.5	25	24.8	16.7	34.3	29	28.4	19.9	38.2
	Grade 3	3	3.0	0.6	8.4	2	2.0	0.2	7.0	3	2.9	0.6	8.4
	Related	61	60.4	50.2	70.0	52	51.5	41.3	61.6	57	55.9	45.7	65.7
VOMITING	Total	22	21.8	14.2	31.1	21	20.8	13.4	30.0	19	18.6	11.6	27.6
	Grade 2*3	12	11.9	6.3	19.8	15	14.9	8.6	23.3	11	10.8	5.5	18.5
	Grade 3	5	5.0	1.6	11.2	7	6.9	2.8	13.8	6	5.9	2.2	12.4
	Related	17	16.8	10.1	25.6	16	15.8	9.3	24.4	13	12.7	7.0	20.8

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		**1**							
Group		**Pooled HRV groups**				**Placebo**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
N		**304**				**101**			
COUGH	**Total**	154	50.7	44.9	56.4	55	54.5	44.2	64.4
	Grade 2*3	36	11.8	8.4	16.0	12	11.9	6.3	19.8
	Grade 3	7	2.3	0.9	4.7	0	0.0	0.0	3.6
	Related	124	40.8	35.2	46.5	43	42.6	32.8	52.8
DIARRHEA	**Total**	27	8.9	5.9	12.7	12	11.9	6.3	19.8
	Grade 2*3	21	6.9	4.3	10.4	8	7.9	3.5	15.0
	Grade 3	7	2.3	0.9	4.7	2	2.0	0.2	7.0
	Related	20	6.6	4.1	10.0	10	9.9	4.9	17.5
IRRITABILITY	**Total**	246	80.9	76.0	85.2	85	84.2	75.6	90.7
	Grade 2*3	100	32.9	27.6	38.5	35	34.7	25.5	44.8
	Grade 3	14	4.6	2.5	7.6	3	3.0	0.6	8.4
	Related	231	76.0	70.8	80.7	78	77.2	67.8	85.0
LOSS OF APPETITE	**Total**	123	40.5	34.9	46.2	35	34.7	25.5	44.8
	Grade 2*3	26	8.6	5.7	12.3	7	6.9	2.8	13.8
	Grade 3	2	0.7	0.1	2.4	0	0.0	0.0	3.6
	Related	105	34.5	29.2	40.2	33	32.7	23.7	42.7
FEVER	**Total**	189	62.2	56.5	67.6	58	57.4	47.2	67.2
	Grade 2*3	82	27.0	22.1	32.3	23	22.8	15.0	32.2
	Grade 3	8	2.6	1.1	5.1	2	2.0	0.2	7.0
	Related	170	55.9	50.1	61.6	55	54.5	44.2	64.4
VOMITING	**Total**	62	20.4	16.0	25.4	19	18.8	11.7	27.8
	Grade 2*3	38	12.5	9.0	16.8	12	11.9	6.3	19.8
	Grade 3	18	5.9	3.5	9.2	4	4.0	1.1	9.8
	Related	46	15.1	11.3	19.7	17	16.8	10.1	25.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		2											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		88				95				90			
COUGH	Total	45	51.1	40.2	61.9	52	54.7	44.2	65.0	54	60.0	49.1	70.2
	Grade 2*3	6	6.8	2.5	14.3	15	15.8	9.1	24.7	13	14.4	7.9	23.4
	Grade 3	1	1.1	0.0	6.2	3	3.2	0.7	9.0	2	2.2	0.3	7.8
	Related	36	40.9	30.5	51.9	43	45.3	35.0	55.8	39	43.3	32.9	54.2
DIARRHEA	Total	4	4.5	1.3	11.2	5	5.3	1.7	11.9	12	13.3	7.1	22.1
	Grade 2*3	3	3.4	0.7	9.6	1	1.1	0.0	5.7	10	11.1	5.5	19.5
	Grade 3	1	1.1	0.0	6.2	0	0.0	0.0	3.8	4	4.4	1.2	11.0
	Related	2	2.3	0.3	8.0	3	3.2	0.7	9.0	8	8.9	3.9	16.8
IRRITABILITY	Total	63	71.6	61.0	80.7	69	72.6	62.5	81.3	67	74.4	64.2	83.1
	Grade 2*3	24	27.3	18.3	37.8	27	28.4	19.6	38.6	32	35.6	25.7	46.3
	Grade 3	4	4.5	1.3	11.2	3	3.2	0.7	9.0	4	4.4	1.2	11.0
	Related	56	63.6	52.7	73.6	60	63.2	52.6	72.8	60	66.7	55.9	76.3
LOSS OF APPETITE	Total	25	28.4	19.3	39.0	26	27.4	18.7	37.5	30	33.3	23.7	44.1
	Grade 2*3	12	13.6	7.2	22.6	7	7.4	3.0	14.6	6	6.7	2.5	13.9
	Grade 3	2	2.3	0.3	8.0	1	1.1	0.0	5.7	0	0.0	0.0	4.0
	Related	21	23.9	15.4	34.1	20	21.1	13.4	30.6	24	26.7	17.9	37.0
FEVER	Total	45	51.1	40.2	61.9	54	56.8	46.3	67.0	44	48.9	38.2	59.7
	Grade 2*3	13	14.8	8.1	23.9	26	27.4	18.7	37.5	19	21.1	13.2	31.0
	Grade 3	1	1.1	0.0	6.2	5	5.3	1.7	11.9	2	2.2	0.3	7.8
	Related	40	45.5	34.8	56.4	47	49.5	39.1	59.9	37	41.1	30.8	52.0
VOMITING	Total	12	13.6	7.2	22.6	15	15.8	9.1	24.7	6	6.7	2.5	13.9
	Grade 2*3	7	8.0	3.3	15.7	11	11.6	5.9	19.8	3	3.3	0.7	9.4
	Grade 3	1	1.1	0.0	6.2	6	6.3	2.4	13.2	2	2.2	0.3	7.8
	Related	9	10.2	4.8	18.5	13	13.7	7.5	22.3	3	3.3	0.7	9.4

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "2 or 3", graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		**2**							
Group		**Pooled HRV groups**				**Placebo**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
N		**273**				**97**			
COUGH	**Total**	151	55.3	49.2	61.3	49	50.5	40.2	60.8
	Grade 2*3	34	12.5	8.8	17.0	13	13.4	7.3	21.8
	Grade 3	6	2.2	0.8	4.7	1	1.0	0.0	5.6
	Related	118	43.2	37.3	49.3	43	44.3	34.2	54.8
DIARRHEA	**Total**	21	7.7	4.8	11.5	13	13.4	7.3	21.8
	Grade 2*3	14	5.1	2.8	8.5	6	6.2	2.3	13.0
	Grade 3	5	1.8	0.6	4.2	2	2.1	0.3	7.3
	Related	13	4.8	2.6	8.0	9	9.3	4.3	16.9
IRRITABILITY	**Total**	199	72.9	67.2	78.1	74	76.3	66.6	84.3
	Grade 2*3	83	30.4	25.0	36.2	31	32.0	22.9	42.2
	Grade 3	11	4.0	2.0	7.1	7	7.2	3.0	14.3
	Related	176	64.5	58.5	70.1	64	66.0	55.7	75.3
LOSS OF APPETITE	**Total**	81	29.7	24.3	35.5	30	30.9	21.9	41.1
	Grade 2*3	25	9.2	6.0	13.2	9	9.3	4.3	16.9
	Grade 3	3	1.1	0.2	3.2	1	1.0	0.0	5.6
	Related	65	23.8	18.9	29.3	26	26.8	18.3	36.8
FEVER	**Total**	143	52.4	46.3	58.4	52	53.6	43.2	63.8
	Grade 2*3	58	21.2	16.5	26.6	24	24.7	16.5	34.5
	Grade 3	8	2.9	1.3	5.7	3	3.1	0.6	8.8
	Related	124	45.4	39.4	51.5	43	44.3	34.2	54.8
VOMITING	**Total**	33	12.1	8.5	16.6	13	13.4	7.3	21.8
	Grade 2*3	21	7.7	4.8	11.5	7	7.2	3.0	14.3
	Grade 3	9	3.3	1.5	6.2	4	4.1	1.1	10.2
	Related	25	9.2	6.0	13.2	8	8.2	3.6	15.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/dose											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		**189**				**196**				**192**			
COUGH	**Total**	99	52.4	45.0	59.7	102	52.0	44.8	59.2	104	54.2	46.8	61.4
	Grade 2*3	19	10.1	6.2	15.3	29	14.8	10.1	20.6	22	11.5	7.3	16.8
	Grade 3	5	2.6	0.9	6.1	4	2.0	0.6	5.1	4	2.1	0.6	5.2
	Related	79	41.8	34.7	49.2	83	42.3	35.3	49.6	80	41.7	34.6	49.0
DIARRHEA	**Total**	12	6.3	3.3	10.8	12	6.1	3.2	10.5	24	12.5	8.2	18.0
	Grade 2*3	8	4.2	1.8	8.2	7	3.6	1.4	7.2	20	10.4	6.5	15.6
	Grade 3	3	1.6	0.3	4.6	3	1.5	0.3	4.4	6	3.1	1.2	6.7
	Related	7	3.7	1.5	7.5	9	4.6	2.1	8.5	17	8.9	5.2	13.8
IRRITABILITY	**Total**	146	77.2	70.6	83.0	146	74.5	67.8	80.4	153	79.7	73.3	85.1
	Grade 2*3	51	27.0	20.8	33.9	64	32.7	26.1	39.7	68	35.4	28.7	42.6
	Grade 3	9	4.8	2.2	8.8	8	4.1	1.8	7.9	8	4.2	1.8	8.0
	Related	135	71.4	64.4	77.8	132	67.3	60.3	73.9	140	72.9	66.0	79.1
LOSS OF APPETITE	**Total**	66	34.9	28.1	42.2	70	35.7	29.0	42.9	68	35.4	28.7	42.6
	Grade 2*3	20	10.6	6.6	15.9	14	7.1	4.0	11.7	17	8.9	5.2	13.8
	Grade 3	2	1.1	0.1	3.8	3	1.5	0.3	4.4	0	0.0	0.0	1.9
	Related	56	29.6	23.2	36.7	56	28.6	22.4	35.4	58	30.2	23.8	37.2
FEVER	**Total**	109	57.7	50.3	64.8	113	57.7	50.4	64.7	110	57.3	50.0	64.4
	Grade 2*3	41	21.7	16.0	28.3	51	26.0	20.0	32.8	48	25.0	19.0	31.7
	Grade 3	4	2.1	0.6	5.3	7	3.6	1.4	7.2	5	2.6	0.9	6.0
	Related	101	53.4	46.1	60.7	99	50.5	43.3	57.7	94	49.0	41.7	56.3
VOMITING	**Total**	34	18.0	12.8	24.2	36	18.4	13.2	24.5	25	13.0	8.6	18.6
	Grade 2*3	19	10.1	6.2	15.3	26	13.3	8.9	18.8	14	7.3	4.0	11.9
	Grade 3	6	3.2	1.2	6.8	13	6.6	3.6	11.1	8	4.2	1.8	8.0
	Related	26	13.8	9.2	19.5	29	14.8	10.1	20.6	16	8.3	4.8	13.2

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/dose							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		577				198			
COUGH	Total	305	52.9	48.7	57.0	104	52.5	45.3	59.6
	Grade 2*3	70	12.1	9.6	15.1	25	12.6	8.3	18.1
	Grade 3	13	2.3	1.2	3.8	1	0.5	0.0	2.8
	Related	242	41.9	37.9	46.1	86	43.4	36.4	50.6
DIARRHEA	Total	48	8.3	6.2	10.9	25	12.6	8.3	18.1
	Grade 2*3	35	6.1	4.3	8.3	14	7.1	3.9	11.6
	Grade 3	12	2.1	1.1	3.6	4	2.0	0.6	5.1
	Related	33	5.7	4.0	7.9	19	9.6	5.9	14.6
IRRITABILITY	Total	445	77.1	73.5	80.5	159	80.3	74.1	85.6
	Grade 2*3	183	31.7	27.9	35.7	66	33.3	26.8	40.4
	Grade 3	25	4.3	2.8	6.3	10	5.1	2.4	9.1
	Related	407	70.5	66.6	74.2	142	71.7	64.9	77.9
LOSS OF APPETITE	Total	204	35.4	31.5	39.4	65	32.8	26.3	39.8
	Grade 2*3	51	8.8	6.7	11.5	16	8.1	4.7	12.8
	Grade 3	5	0.9	0.3	2.0	1	0.5	0.0	2.8
	Related	170	29.5	25.8	33.4	59	29.8	23.5	36.7
FEVER	Total	332	57.5	53.4	61.6	110	55.6	48.3	62.6
	Grade 2*3	140	24.3	20.8	28.0	47	23.7	18.0	30.3
	Grade 3	16	2.8	1.6	4.5	5	2.5	0.8	5.8
	Related	294	51.0	46.8	55.1	98	49.5	42.3	56.7
VOMITING	Total	95	16.5	13.5	19.7	32	16.2	11.3	22.0
	Grade 2*3	59	10.2	7.9	13.0	19	9.6	5.9	14.6
	Grade 3	27	4.7	3.1	6.7	8	4.0	1.8	7.8
	Related	71	12.3	9.7	15.3	25	12.6	8.3	18.1

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/subject											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		101				101				102			
COUGH	Total	76	75.2	65.7	83.3	72	71.3	61.4	79.9	75	73.5	63.9	81.8
	Grade 2*3	19	18.8	11.7	27.8	23	22.8	15.0	32.2	22	21.6	14.0	30.8
	Grade 3	5	5.0	1.6	11.2	3	3.0	0.6	8.4	4	3.9	1.1	9.7
	Related	60	59.4	49.2	69.1	62	61.4	51.2	70.9	64	62.7	52.6	72.1
DIARRHEA	Total	12	11.9	6.3	19.8	12	11.9	6.3	19.8	21	20.6	13.2	29.7
	Grade 2*3	8	7.9	3.5	15.0	7	6.9	2.8	13.8	17	16.7	10.0	25.3
	Grade 3	3	3.0	0.6	8.4	3	3.0	0.6	8.4	6	5.9	2.2	12.4
	Related	7	6.9	2.8	13.8	9	8.9	4.2	16.2	16	15.7	9.2	24.2
IRRITABILITY	Total	89	88.1	80.2	93.7	87	86.1	77.8	92.2	93	91.2	83.9	95.9
	Grade 2*3	38	37.6	28.2	47.8	48	47.5	37.5	57.7	50	49.0	39.0	59.1
	Grade 3	8	7.9	3.5	15.0	7	6.9	2.8	13.8	6	5.9	2.2	12.4
	Related	86	85.1	76.7	91.4	81	80.2	71.1	87.5	89	87.3	79.2	93.0
LOSS OF APPETITE	Total	51	50.5	40.4	60.6	55	54.5	44.2	64.4	50	49.0	39.0	59.1
	Grade 2*3	18	17.8	10.9	26.7	12	11.9	6.3	19.8	13	12.7	7.0	20.8
	Grade 3	2	2.0	0.2	7.0	3	3.0	0.6	8.4	0	0.0	0.0	3.6
	Related	44	43.6	33.7	53.8	46	45.5	35.6	55.8	44	43.1	33.4	53.3
FEVER	Total	73	72.3	62.5	80.7	80	79.2	70.0	86.6	76	74.5	64.9	82.6
	Grade 2*3	36	35.6	26.4	45.8	43	42.6	32.8	52.8	41	40.2	30.6	50.4
	Grade 3	4	4.0	1.1	9.8	7	6.9	2.8	13.8	4	3.9	1.1	9.7
	Related	70	69.3	59.3	78.1	71	70.3	60.4	79.0	67	65.7	55.6	74.8
VOMITING	Total	29	28.7	20.1	38.6	32	31.7	22.8	41.7	22	21.6	14.0	30.8
	Grade 2*3	16	15.8	9.3	24.4	25	24.8	16.7	34.3	13	12.7	7.0	20.8
	Grade 3	6	5.9	2.2	12.5	13	12.9	7.0	21.0	7	6.9	2.8	13.6
	Related	21	20.8	13.4	30.0	27	26.7	18.4	36.5	15	14.7	8.5	23.1

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 72 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/subject							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		304				101			
COUGH	Total	223	73.4	68.0	78.2	71	70.3	60.4	79.0
	Grade 2*3	64	21.1	16.6	26.1	21	20.8	13.4	30.0
	Grade 3	12	3.9	2.1	6.8	1	1.0	0.0	5.4
	Related	186	61.2	55.5	66.7	64	63.4	53.2	72.7
DIARRHEA	Total	45	14.8	11.0	19.3	23	22.8	15.0	32.2
	Grade 2*3	32	10.5	7.3	14.5	14	13.9	7.8	22.2
	Grade 3	12	3.9	2.1	6.8	4	4.0	1.1	9.8
	Related	32	10.5	7.3	14.5	17	16.8	10.1	25.6
IRRITABILITY	Total	269	88.5	84.4	91.8	93	92.1	85.0	96.5
	Grade 2*3	136	44.7	39.1	50.5	49	48.5	38.4	58.7
	Grade 3	21	6.9	4.3	10.4	8	7.9	3.5	15.0
	Related	256	84.2	79.6	88.1	85	84.2	75.6	90.7
LOSS OF APPETITE	Total	156	51.3	45.5	57.1	49	48.5	38.4	58.7
	Grade 2*3	43	14.1	10.4	18.6	14	13.9	7.8	22.2
	Grade 3	5	1.6	0.5	3.8	1	1.0	0.0	5.4
	Related	134	44.1	38.4	49.9	47	46.5	36.5	56.7
FEVER	Total	229	75.3	70.1	80.1	77	76.2	66.7	84.1
	Grade 2*3	120	39.5	33.9	45.2	37	36.6	27.3	46.8
	Grade 3	15	4.9	2.8	8.0	5	5.0	1.6	11.2
	Related	208	68.4	62.9	73.6	69	68.3	58.3	77.2
VOMITING	Total	83	27.3	22.4	32.7	26	25.7	17.6	35.4
	Grade 2*3	54	17.8	13.6	22.5	17	16.8	10.1	25.6
	Grade 3	26	8.6	5.7	12.3	8	7.9	3.5	15.0
	Related	63	20.7	16.3	25.7	21	20.8	13.4	30.0

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73: Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		1											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		243				243				244			
COUGH	Total	146	60.1	53.6	66.3	135	55.6	49.1	61.9	153	62.7	56.3	68.8
	Grade 2*3	104	42.8	36.5	49.3	94	38.7	32.5	45.1	102	41.8	35.5	48.3
	Grade 3	34	14.0	9.9	19.0	41	16.9	12.4	22.2	41	16.8	12.3	22.1
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5
DIARRHEA	Total	3	1.2	0.3	3.6	3	1.2	0.3	3.6	3	1.2	0.3	3.6
	Grade 2*3	2	0.8	0.1	2.9	3	1.2	0.3	3.6	3	1.2	0.3	3.6
	Grade 3	1	0.4	0.0	2.3	1	0.4	0.0	2.3	3	1.2	0.3	3.6
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5
IRRITABILITY	Total	134	55.1	48.7	61.5	143	58.8	52.4	65.1	138	56.6	50.1	62.9
	Grade 2*3	107	44.0	37.7	50.5	111	45.7	39.3	52.2	102	41.8	35.5	48.3
	Grade 3	43	17.7	13.1	23.1	43	17.7	13.1	23.1	48	19.7	14.9	25.2
	Related	1	0.4	0.0	2.3	0	0.0	0.0	1.5	0	0.0	0.0	1.5
LOSS OF APPETITE	Total	75	30.9	25.1	37.1	75	30.9	25.1	37.1	75	30.7	25.0	36.9
	Grade 2*3	18	7.4	4.4	11.5	25	10.3	6.8	14.8	35	14.3	10.2	19.4
	Grade 3	2	0.8	0.1	2.9	4	1.6	0.5	4.2	10	4.1	2.0	7.4
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5
FEVER	Total	119	49.0	42.5	55.4	136	56.0	49.5	62.3	126	51.6	45.2	58.1
	Grade 2*3	24	9.9	6.4	14.3	19	7.8	4.8	11.9	23	9.4	6.1	13.8
	Grade 3	1	0.4	0.0	2.3	2	0.8	0.1	2.9	1	0.4	0.0	2.3
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5
VOMITING	Total	20	8.2	5.1	12.4	32	13.2	9.2	18.1	25	10.2	6.7	14.8
	Grade 2*3	8	3.3	1.4	6.4	17	7.0	4.1	11.0	12	4.9	2.6	8.4
	Grade 3	2	0.8	0.1	2.9	9	3.7	1.7	6.9	6	2.5	0.9	5.3
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		1							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		730				242			
COUGH	Total	434	59.5	55.8	63.0	152	62.8	56.4	68.9
	Grade 2*3	300	41.1	37.5	44.8	109	45.0	38.7	51.5
	Grade 3	116	15.9	13.3	18.7	28	11.6	7.8	16.3
	Related	0	0.0	0.0	0.5	1	0.4	0.0	2.3
DIARRHEA	Total	9	1.2	0.6	2.3	5	2.1	0.7	4.8
	Grade 2*3	8	1.1	0.5	2.1	3	1.2	0.3	3.6
	Grade 3	5	0.7	0.2	1.6	2	0.8	0.1	3.0
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5
IRRITABILITY	Total	415	56.8	53.2	60.5	153	63.2	56.8	69.3
	Grade 2*3	320	43.8	40.2	47.5	122	50.4	43.9	56.9
	Grade 3	134	18.4	15.6	21.4	52	21.5	16.5	27.2
	Related	1	0.1	0.0	0.8	0	0.0	0.0	1.5
LOSS OF APPETITE	Total	225	30.8	27.5	34.3	86	35.5	29.5	41.9
	Grade 2*3	78	10.7	8.5	13.2	31	12.8	8.9	17.7
	Grade 3	16	2.2	1.3	3.5	6	2.5	0.9	5.3
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5
FEVER	Total	381	52.2	48.5	55.9	145	59.9	53.4	66.1
	Grade 2*3	66	9.0	7.1	11.4	32	13.2	9.2	18.2
	Grade 3	4	0.5	0.1	1.4	3	1.2	0.3	3.6
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5
VOMITING	Total	77	10.5	8.4	13.0	21	8.7	5.5	13.0
	Grade 2*3	37	5.1	3.6	6.9	10	4.1	2.0	7.5
	Grade 3	17	2.3	1.4	3.7	4	1.7	0.5	4.2
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		2											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		235				231				233			
COUGH	Total	140	59.6	53.0	65.9	138	59.7	53.1	66.1	151	64.8	58.3	70.9
	Grade 2*3	91	38.7	32.5	45.3	88	38.1	31.8	44.7	105	45.1	38.6	51.7
	Grade 3	35	14.9	10.6	20.1	32	13.9	9.7	19.0	41	17.6	12.9	23.1
	Related	0	0.0	0.0	1.6	1	0.4	0.0	2.4	0	0.0	0.0	1.6
DIARRHEA	Total	3	1.3	0.3	3.7	1	0.4	0.0	2.4	4	1.7	0.5	4.3
	Grade 2*3	3	1.3	0.3	3.7	1	0.4	0.0	2.4	4	1.7	0.5	4.3
	Grade 3	2	0.9	0.1	3.0	1	0.4	0.0	2.4	3	1.3	0.3	3.7
	Related	0	0.0	0.0	1.6	0	0.0	0.0	1.6	0	0.0	0.0	1.6
IRRITABILITY	Total	109	46.4	39.9	53.0	113	48.9	42.3	55.6	123	52.8	46.2	59.3
	Grade 2*3	75	31.9	26.0	38.3	78	33.8	27.7	40.3	94	40.3	34.0	46.9
	Grade 3	33	14.0	9.9	19.2	28	12.1	8.2	17.0	39	16.7	12.2	22.2
	Related	0	0.0	0.0	1.6	0	0.0	0.0	1.6	0	0.0	0.0	1.6
LOSS OF APPETITE	Total	68	28.9	23.2	35.2	75	32.5	26.5	38.9	75	32.2	26.2	38.6
	Grade 2*3	28	11.9	8.1	16.8	31	13.4	9.3	18.5	37	15.9	11.4	21.2
	Grade 3	9	3.8	1.8	7.1	9	3.9	1.8	7.3	1	0.4	0.0	2.4
	Related	0	0.0	0.0	1.6	0	0.0	0.0	1.6	0	0.0	0.0	1.6
FEVER	Total	117	49.8	43.2	56.4	129	55.8	49.2	62.4	119	51.1	44.5	57.7
	Grade 2*3	35	14.9	10.6	20.1	44	19.0	14.2	24.7	37	15.9	11.4	21.2
	Grade 3	1	0.4	0.0	2.3	2	0.9	0.1	3.1	5	2.1	0.7	4.9
	Related	0	0.0	0.0	1.6	1	0.4	0.0	2.4	0	0.0	0.0	1.6
VOMITING	Total	10	4.3	2.1	7.7	18	7.8	4.7	12.0	25	10.7	7.1	15.4
	Grade 2*3	6	2.6	0.9	5.5	8	3.5	1.5	6.7	17	7.3	4.3	11.4
	Grade 3	3	1.3	0.3	3.7	5	2.2	0.7	5.0	9	3.9	1.8	7.2
	Related	0	0.0	0.0	1.6	0	0.0	0.0	1.6	0	0.0	0.0	1.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		**2**							
Group		**Pooled HRV groups**				**Placebo**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
N		**699**				**234**			
COUGH	**Total**	429	61.4	57.7	65.0	144	61.5	55.0	67.8
	Grade 2*3	284	40.6	37.0	44.4	110	47.0	40.5	53.6
	Grade 3	108	15.5	12.9	18.3	32	13.7	9.5	18.8
	Related	1	0.1	0.0	0.8	0	0.0	0.0	1.6
DIARRHEA	**Total**	8	1.1	0.5	2.2	5	2.1	0.7	4.9
	Grade 2*3	8	1.1	0.5	2.2	5	2.1	0.7	4.9
	Grade 3	6	0.9	0.3	1.9	3	1.3	0.3	3.7
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.6
IRRITABILITY	**Total**	345	49.4	45.6	53.1	123	52.6	46.0	59.1
	Grade 2*3	247	35.3	31.8	39.0	87	37.2	31.0	43.7
	Grade 3	100	14.3	11.8	17.1	27	11.5	7.7	16.3
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.6
LOSS OF APPETITE	**Total**	218	31.2	27.8	34.8	73	31.2	25.3	37.6
	Grade 2*3	96	13.7	11.3	16.5	39	16.7	12.1	22.1
	Grade 3	19	2.7	1.6	4.2	10	4.3	2.1	7.7
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.6
FEVER	**Total**	365	52.2	48.4	56.0	135	57.7	51.1	64.1
	Grade 2*3	116	16.6	13.9	19.6	28	12.0	8.1	16.8
	Grade 3	8	1.1	0.5	2.2	1	0.4	0.0	2.4
	Related	1	0.1	0.0	0.8	0	0.0	0.0	1.6
VOMITING	**Total**	53	7.6	5.7	9.8	20	8.5	5.3	12.9
	Grade 2*3	31	4.4	3.0	6.2	11	4.7	2.4	8.3
	Grade 3	17	2.4	1.4	3.9	5	2.1	0.7	4.9
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.6

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/dose											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		478				474				477			
COUGH	Total	286	59.8	55.3	64.3	273	57.6	53.0	62.1	304	63.7	59.2	68.1
	Grade 2*3	195	40.8	36.4	45.4	182	38.4	34.0	42.9	207	43.4	38.9	48.0
	Grade 3	69	14.4	11.4	17.9	73	15.4	12.3	19.0	82	17.2	13.9	20.9
	Related	0	0.0	0.0	0.8	1	0.2	0.0	1.2	0	0.0	0.0	0.8
DIARRHEA	Total	6	1.3	0.5	2.7	4	0.8	0.2	2.1	7	1.5	0.6	3.0
	Grade 2*3	5	1.0	0.3	2.4	4	0.8	0.2	2.1	7	1.5	0.6	3.0
	Grade 3	3	0.6	0.1	1.8	2	0.4	0.1	1.5	6	1.3	0.5	2.7
	Related	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.8
IRRITABILITY	Total	243	50.8	46.3	55.4	256	54.0	49.4	58.6	261	54.7	50.1	59.2
	Grade 2*3	182	38.1	33.7	42.6	189	39.9	35.4	44.4	196	41.1	36.6	45.7
	Grade 3	76	15.9	12.7	19.5	71	15.0	11.9	18.5	87	18.2	14.9	22.0
	Related	1	0.2	0.0	1.2	0	0.0	0.0	0.8	0	0.0	0.0	0.8
LOSS OF APPETITE	Total	143	29.9	25.8	34.2	150	31.6	27.5	36.0	150	31.4	27.3	35.8
	Grade 2*3	46	9.6	7.1	12.6	56	11.8	9.0	15.1	72	15.1	12.0	18.6
	Grade 3	11	2.3	1.2	4.1	13	2.7	1.5	4.6	11	2.3	1.2	4.1
	Related	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.8
FEVER	Total	236	49.4	44.8	54.0	265	55.9	51.3	60.4	245	51.4	46.8	55.9
	Grade 2*3	59	12.3	9.5	15.6	63	13.3	10.4	16.7	60	12.6	9.7	15.9
	Grade 3	2	0.4	0.1	1.5	4	0.8	0.2	2.1	6	1.3	0.5	2.7
	Related	0	0.0	0.0	0.8	1	0.2	0.0	1.2	0	0.0	0.0	0.8
VOMITING	Total	30	6.3	4.3	8.8	50	10.5	7.9	13.7	50	10.5	7.9	13.6
	Grade 2*3	14	2.9	1.6	4.9	25	5.3	3.4	7.7	29	6.1	4.1	8.6
	Grade 3	5	1.0	0.3	2.4	14	3.0	1.6	4.9	15	3.1	1.8	5.1
	Related	0	0.0	0.0	0.8	0	0.0	0.0	0.8	0	0.0	0.0	0.8

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		**Overall/dose**							
Group		**Pooled HRV groups**				**Placebo**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
N		1429				476			
COUGH	**Total**	863	60.4	57.8	62.9	296	62.2	57.7	66.6
	Grade 2*3	584	40.9	38.3	43.5	219	46.0	41.5	50.6
	Grade 3	224	15.7	13.8	17.7	60	12.6	9.8	15.9
	Related	1	0.1	0.0	0.4	1	0.2	0.0	1.2
DIARRHEA	**Total**	17	1.2	0.7	1.9	10	2.1	1.0	3.8
	Grade 2*3	16	1.1	0.6	1.8	8	1.7	0.7	3.3
	Grade 3	11	0.8	0.4	1.4	5	1.1	0.3	2.4
	Related	0	0.0	0.0	0.3	0	0.0	0.0	0.8
IRRITABILITY	**Total**	760	53.2	50.6	55.8	276	58.0	53.4	62.5
	Grade 2*3	567	39.7	37.1	42.3	209	43.9	39.4	48.5
	Grade 3	234	16.4	14.5	18.4	79	16.6	13.4	20.2
	Related	1	0.1	0.0	0.4	0	0.0	0.0	0.8
LOSS OF APPETITE	**Total**	443	31.0	28.6	33.5	159	33.4	29.2	37.8
	Grade 2*3	174	12.2	10.5	14.0	70	14.7	11.6	18.2
	Grade 3	35	2.4	1.7	3.4	16	3.4	1.9	5.4
	Related	0	0.0	0.0	0.3	0	0.0	0.0	0.8
FEVER	**Total**	746	52.2	49.6	54.8	280	58.8	54.3	63.3
	Grade 2*3	182	12.7	11.1	14.6	60	12.6	9.8	15.9
	Grade 3	12	0.8	0.4	1.5	4	0.8	0.2	2.1
	Related	1	0.1	0.0	0.4	0	0.0	0.0	0.8
VOMITING	**Total**	130	9.1	7.7	10.7	41	8.6	6.3	11.5
	Grade 2*3	68	4.8	3.7	6.0	21	4.4	2.8	6.7
	Grade 3	34	2.4	1.7	3.3	9	1.9	0.9	3.6
	Related	0	0.0	0.0	0.3	0	0.0	0.0	0.8

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/subject											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		243				243				244			
COUGH	Total	186	76.5	70.7	81.7	181	74.5	68.5	79.8	187	76.6	70.8	81.8
	Grade 2*3	138	56.8	50.3	63.1	139	57.2	50.7	63.5	145	59.4	53.0	65.6
	Grade 3	62	25.5	20.2	31.5	64	26.3	20.9	32.3	67	27.5	22.0	33.5
	Related	0	0.0	0.0	1.5	1	0.4	0.0	2.3	0	0.0	0.0	1.5
DIARRHEA	Total	6	2.5	0.9	5.3	4	1.6	0.5	4.2	7	2.9	1.2	5.8
	Grade 2*3	5	2.1	0.7	4.7	4	1.6	0.5	4.2	7	2.9	1.2	5.8
	Grade 3	3	1.2	0.3	3.6	2	0.8	0.1	2.9	6	2.5	0.9	5.3
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5
IRRITABILITY	Total	159	65.4	59.1	71.4	172	70.8	64.6	76.4	167	68.4	62.2	74.2
	Grade 2*3	133	54.7	48.2	61.1	141	58.0	51.5	64.3	132	54.1	47.6	60.5
	Grade 3	61	25.1	19.8	31.0	60	24.7	19.4	30.6	64	26.2	20.8	32.2
	Related	1	0.4	0.0	2.3	0	0.0	0.0	1.5	0	0.0	0.0	1.5
LOSS OF APPETITE	Total	101	41.6	35.3	48.0	113	46.5	40.1	53.0	109	44.7	38.3	51.1
	Grade 2*3	40	16.5	12.0	21.7	49	20.2	15.3	25.8	61	25.0	19.7	30.9
	Grade 3	9	3.7	1.7	6.9	12	4.9	2.6	8.5	11	4.5	2.3	7.9
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5
FEVER	Total	166	68.3	62.1	74.1	181	74.5	68.5	79.8	167	68.4	62.2	74.2
	Grade 2*3	47	19.3	14.6	24.9	57	23.5	18.3	29.3	51	20.9	16.0	26.5
	Grade 3	2	0.8	0.1	2.9	4	1.6	0.5	4.2	6	2.5	0.9	5.3
	Related	0	0.0	0.0	1.5	1	0.4	0.0	2.3	0	0.0	0.0	1.5
VOMITING	Total	28	11.5	7.8	16.2	45	18.5	13.8	24.0	45	18.4	13.8	23.9
	Grade 2*3	12	4.9	2.6	8.5	23	9.5	6.1	13.9	26	10.7	7.1	15.2
	Grade 3	5	2.1	0.7	4.7	14	5.8	3.2	9.5	14	5.7	3.2	9.4
	Related	0	0.0	0.0	1.5	0	0.0	0.0	1.5	0	0.0	0.0	1.5

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 73 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/subject							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		730				242			
COUGH	Total	554	75.9	72.6	79.0	195	80.6	75.0	85.4
	Grade 2*3	422	57.8	54.1	61.4	160	66.1	59.8	72.1
	Grade 3	193	26.4	23.3	29.8	51	21.1	16.1	26.8
	Related	1	0.1	0.0	0.8	1	0.4	0.0	2.3
DIARRHEA	Total	17	2.3	1.4	3.7	9	3.7	1.7	6.9
	Grade 2*3	16	2.2	1.3	3.5	7	2.9	1.2	5.9
	Grade 3	11	1.5	0.8	2.7	4	1.7	0.5	4.2
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5
IRRITABILITY	Total	498	68.2	64.7	71.6	175	72.3	66.2	77.9
	Grade 2*3	406	55.6	51.9	59.3	146	60.3	53.9	66.5
	Grade 3	185	25.3	22.2	28.7	68	28.1	22.5	34.2
	Related	1	0.1	0.0	0.8	0	0.0	0.0	1.5
LOSS OF APPETITE	Total	323	44.2	40.6	47.9	115	47.5	41.1	54.0
	Grade 2*3	150	20.5	17.7	23.7	57	23.6	18.4	29.4
	Grade 3	32	4.4	3.0	6.1	16	6.6	3.8	10.5
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5
FEVER	Total	514	70.4	67.0	73.7	184	76.0	70.1	81.3
	Grade 2*3	155	21.2	18.3	24.4	54	22.3	17.2	28.1
	Grade 3	12	1.6	0.9	2.9	4	1.7	0.5	4.2
	Related	1	0.1	0.0	0.8	0	0.0	0.0	1.5
VOMITING	Total	118	16.2	13.6	19.0	38	15.7	11.4	20.9
	Grade 2*3	61	8.4	6.5	10.6	19	7.9	4.8	12.0
	Grade 3	33	4.5	3.1	6.3	9	3.7	1.7	6.9
	Related	0	0.0	0.0	0.5	0	0.0	0.0	1.5

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 74: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 194				HRV_5.2 N = 196				HRV_5.8 N = 194				Pooled HRV groups N = 584				Placebo N = 194			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		153	78.9	72.4	84.4	154	78.6	72.2	84.1	146	75.3	68.6	81.2	453	77.6	74	80.9	153	78.9	72.4	84.4
Application site (1820)	Injection site reaction (0058)	7	3.6	1.5	7.3	5	2.6	0.8	5.9	4	2.1	0.6	5.2	16	2.7	1.6	4.4	7	3.6	1.5	7.3
	Otitis externa (0059)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.8	1	0.2	0	1	0	0	0	1.9
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	1	0.5	0	2.8
	Allergic reaction (0712)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Allergy (1058)	3	1.5	0.3	4.5	12	6.1	3.2	10.5	5	2.6	0.8	5.9	20	3.4	2.1	5.2	9	4.6	2.1	8.6
	Fever (0725)	33	17	12	23.1	26	13.3	8.9	18.8	34	17.5	12.5	23.6	93	15.9	13	19.1	23	11.9	7.7	17.3
	Injury (9001)	2	1	0.1	3.7	0	0	0	1.9	0	0	0	1.9	2	0.3	0	1.2	0	0	0	1.9
	Pallor (0220)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Cardiovascular general (1010)	Cyanosis (0501)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
Fetal (1500)	Vascular malformation peripheral (0764)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 74 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 194				HRV_5.2 N = 196				HRV_5.8 N = 194				Pooled HRV groups N = 584				Placebo N = 194			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Gastrointestinal system (600)	Abdominal pain (0268)	1	0.5	0	2.8	1	0.5	0	2.8	1	0.5	0	2.8	3	0.5	0.1	1.5	1	0.5	0	2.8
	Anorexia (0165)	4	2.1	0.6	5.2	5	2.6	0.8	5.9	2	1	0.1	3.7	11	1.9	0.9	3.3	5	2.6	0.8	5.9
	Constipation (0204)	3	1.5	0.3	4.5	0	0	0	1.9	2	1	0.1	3.7	5	0.9	0.3	2	4	2.1	0.6	5.2
	Gastroenteritis (0293)	3	1.5	0.3	4.5	5	2.6	0.8	5.9	1	0.5	0	2.8	9	1.5	0.7	2.9	4	2.1	0.6	5.2
	Gastroesophageal reflux (1149)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Gastrointestinal disorder nos (1262)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.8	1	0.2	0	1	1	0.5	0	2.8
	Stomatitis (0327)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Vomiting (0228)	3	1.5	0.3	4.5	4	2	0.6	5.1	5	2.6	0.8	5.9	12	2.1	1.1	3.6	8	4.1	1.8	8
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Earache (0260)	2	1	0.1	3.7	1	0.5	0	2.8	1	0.5	0	2.8	4	0.7	0.2	1.7	2	1	0.1	3.7
Neoplasm (1700)	Neoplasm nos (1259)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
Psychiatric (500)	Nervousness (0188)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Red blood cell (1210)	Anemia (0544)	1	0.5	0	2.8	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
Reproductive female (1420)	Leukorrhea (0654)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.8	1	0.2	0	1	0	0	0	1.9

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 74 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 194				HRV_5.2 N = 196				HRV_5.8 N = 194				Pooled HRV groups N = 584				Placebo N = 194			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Resistance mechanism (1830)	Abscess (0887)	1	0.5	0	2.8	1	0.5	0	2.8	2	1	0.1	3.7	4	0.7	0.2	1.7	0	0	0	1.9
	Infection (0736)	10	5.2	2.5	9.3	8	4.1	1.8	7.9	10	5.2	2.5	9.3	28	4.8	3.2	6.9	15	7.7	4.4	12.4
	Infection bacterial (0738)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Infection viral (0740)	99	51	43.8	58.3	99	50.5	43.3	57.7	94	48.5	41.2	55.7	292	50	45.9	54.1	101	52.1	44.8	59.3
	Moniliasis (0741)	1	0.5	0	2.8	7	3.6	1.4	7.2	2	1	0.1	3.7	10	1.7	0.8	3.1	2	1	0.1	3.7
	Otitis media (0750)	0	0	0	1.9	6	3.1	1.1	6.5	2	1	0.1	3.7	8	1.4	0.6	2.7	2	1	0.1	3.7
	Upper resp tract infection (0543)	20	10.3	6.4	15.5	12	6.1	3.2	10.5	14	7.2	4	11.8	46	7.9	5.8	10.4	15	7.7	4.4	12.4
Respiratory system (1100)	Asthma (1367)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Bronchitis (0805)	12	6.2	3.2	10.6	14	7.1	4	11.7	10	5.2	2.5	9.3	36	6.2	4.4	8.4	4	2.1	0.6	5.2
	Bronchospasm (0511)	1	0.5	0	2.8	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Coughing (0513)	24	12.4	8.1	17.8	23	11.7	7.6	17.1	23	11.9	7.7	17.3	70	12	9.5	14.9	15	7.7	4.4	12.4
	Dyspnea (0514)	0	0	0	1.9	1	0.5	0	2.8	1	0.5	0	2.8	2	0.3	0	1.2	1	0.5	0	2.8
	Laryngitis (0521)	1	0.5	0	2.8	1	0.5	0	2.8	1	0.5	0	2.8	3	0.5	0.1	1.5	0	0	0	1.9
	Pharyngitis (0523)	3	1.5	0.3	4.5	8	4.1	1.8	7.9	4	2.1	0.6	5.2	15	2.6	1.4	4.2	4	2.1	0.6	5.2
Respiratory system (1100)	Pneumonia (0528)	4	2.1	0.6	5.2	4	2	0.6	5.1	4	2.1	0.6	5.2	12	2.1	1.1	3.6	3	1.5	0.3	4.5
	Respiratory disorder (0536)	0	0	0	1.9	6	3.1	1.1	6.5	1	0.5	0	2.8	7	1.2	0.5	2.5	2	1	0.1	3.7
	Rhinitis (0539)	8	4.1	1.8	8	15	7.7	4.3	12.3	11	5.7	2.9	9.9	34	5.8	4.1	8	14	7.2	4	11.8
	Sputum increased (0541)	3	1.5	0.3	4.5	8	4.1	1.8	7.9	2	1	0.1	3.7	13	2.2	1.2	3.8	3	1.5	0.3	4.5
Secondary term (2000)	Varicella (1516)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 74 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 194				HRV_5.2 N = 196				HRV_5.8 N = 194				Pooled HRV groups N = 584				Placebo N = 194			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Skin and appendages (100)	Alopecia (0002)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Dermatitis (0007)	1	0.5	0	2.8	3	1.5	0.3	4.4	2	1	0.1	3.7	6	1	0.4	2.2	0	0	0	1.9
	Furunculosis (0016)	3	1.5	0.3	4.5	1	0.5	0	2.8	1	0.5	0	2.8	5	0.9	0.3	2	0	0	0	1.9
	Pruritus (0024)	0	0	0	1.9	3	1.5	0.3	4.4	2	1	0.1	3.7	5	0.9	0.3	2	0	0	0	1.9
	Rash (0027)	1	0.5	0	2.8	1	0.5	0	2.8	0	0	0	1.9	2	0.3	0	1.2	0	0	0	1.9
	Rash erythematous (0028)	2	1	0.1	3.7	0	0	0	1.9	0	0	0	1.9	2	0.3	0	1.2	1	0.5	0	2.8
	Rash maculo-papular (0030)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Rash pustular (0032)	0	0	0	1.9	1	0.5	0	2.8	2	1	0.1	3.7	3	0.5	0.1	1.5	0	0	0	1.9
Skin and appendages (100)	Seborrhea (0033)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Skin disorder (0037)	6	3.1	1.1	6.6	8	4.1	1.8	7.9	9	4.6	2.1	8.6	23	3.9	2.5	5.9	10	5.2	2.5	9.3
	Sweat gland disorder(1166)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.8	1	0.2	0	1	0	0	0	1.9
Urinary system (1300)	Dysuria (0601)	0	0	0	1.9	1	0.5	0	2.8	2	1	0.1	3.7	3	0.5	0.1	1.5	0	0	0	1.9
Vision (431)	Blepharitis (1007)	1	0.5	0	2.8	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Conjunctivitis (0238)	3	1.5	0.3	4.5	4	2	0.6	5.1	3	1.5	0.3	4.5	10	1.7	0.8	3.1	3	1.5	0.3	4.5
White cell and reticuloendothelial system (1220)	Lymphadenopathy cervical (0578)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.8	1	0.2	0	1	0	0	0	1.9

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 75: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 101				HRV_5.2 N = 101				HRV_5.8 N = 102				Pooled HRV groups N = 304				Placebo N = 101			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		82	81.2	72.2	88.3	90	89.1	81.3	94.4	87	85.3	76.9	91.5	259	85.2	80.7	89	87	86.1	77.8	92.2
Application site (1820)	Dermatitis contact (0049)	4	4	1.1	9.8	7	6.9	2.8	13.8	4	3.9	1.1	9.7	15	4.9	2.8	8	5	5	1.6	11.2
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	3.6	1	1	0	5.4	1	1	0	5.3	2	0.7	0.1	2.4	0	0	0	3.6
	Death, nos (0722)	0	0	0	3.6	0	0	0	3.6	1	1	0	5.3	1	0.3	0	1.8	0	0	0	3.6
	Edema generalised (0400)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Fever (0725)	11	10.9	5.6	18.7	18	17.8	10.9	26.7	11	10.8	5.5	18.5	40	13.2	9.6	17.5	18	17.8	10.9	26.7
	Injury (9001)	1	1	0	5.4	0	0	0	3.6	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Fever convulsions (1357)	0	0	0	3.6	0	0	0	3.6	1	1	0	5.3	1	0.3	0	1.8	0	0	0	3.6
Gastrointestinal system (600)	Abdominal pain (0268)	28	27.7	19.3	37.5	25	24.8	16.7	34.3	22	21.6	14	30.8	75	24.7	19.9	29.9	22	21.8	14.2	31.1
	Anorexia (0165)	17	16.8	10.1	25.6	16	15.8	9.3	24.4	12	11.8	6.2	19.6	45	14.8	11	19.3	21	20.8	13.4	30
	Constipation (0204)	8	7.9	3.5	15	10	9.9	4.9	17.5	8	7.8	3.4	14.9	26	8.6	5.7	12.3	2	2	0.2	7
	Gastroesophageal reflux (1149)	4	4	1.1	9.8	6	5.9	2.2	12.5	7	6.9	2.8	13.6	17	5.6	3.3	8.8	3	3	0.6	8.4
	Vomiting (0228)	11	10.9	5.6	18.7	13	12.9	7	21	11	10.8	5.5	18.5	35	11.5	8.2	15.6	12	11.9	6.3	19.8
Psychiatric (500)	Nervousness (0188)	30	29.7	21	39.6	26	25.7	17.6	35.4	30	29.4	20.8	39.3	86	28.3	23.3	33.7	33	32.7	23.7	42.7

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 75 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 101				HRV_5.2 N = 101				HRV_5.8 N = 102				Pooled HRV groups N = 304				Placebo N = 101			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Resistance mechanism (1830)	Infection bacterial (0738)	0	0	0	3.6	1	1	0	5.4	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
	Infection viral (0740)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Moniliasis (0741)	5	5	1.6	11.2	5	5	1.6	11.2	1	1	0	5.3	11	3.6	1.8	6.4	3	3	0.6	8.4
	Otitis media (0750)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Upper resp tract infection (0543)	21	20.8	13.4	30	24	23.8	15.9	33.3	30	29.4	20.8	39.3	75	24.7	19.9	29.9	25	24.8	16.7	34.3
Respiratory system (1100)	Bronchitis (0805)	1	1	0	5.4	1	1	0	5.4	0	0	0	3.6	2	0.7	0.1	2.4	0	0	0	3.6
	Coughing (0513)	6	5.9	2.2	12.5	2	2	0.2	7	6	5.9	2.2	12.4	14	4.6	2.5	7.6	5	5	1.6	11.2
	Laryngitis (0521)	0	0	0	3.6	1	1	0	5.4	1	1	0	5.3	2	0.7	0.1	2.4	2	2	0.2	7
	Pharyngitis (0523)	52	51.5	41.3	61.6	64	63.4	53.2	72.7	59	57.8	47.7	67.6	175	57.6	51.8	63.2	62	61.4	51.2	70.9
	Pneumonia (0528)	4	4	1.1	9.8	10	9.9	4.9	17.5	4	3.9	1.1	9.7	18	5.9	3.5	9.2	8	7.9	3.5	15
Secondary term (2000)	Varicella (1516)	1	1	0	5.4	0	0	0	3.6	0	0	0	3.6	1	0.3	0	1.8	4	4	1.1	9.8
Skin and appendages (100)	Dermatitis (0007)	1	1	0	5.4	1	1	0	5.4	2	2	0.2	6.9	4	1.3	0.4	3.3	0	0	0	3.6
	Photosensitivity reaction (0022)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Rash erythematous (0028)	0	0	0	3.6	1	1	0	5.4	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
	Rash maculo-papular (0030)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Sweat gland disorder (1166)	1	1	0	5.4	1	1	0	5.4	1	1	0	5.3	3	1	0.2	2.9	0	0	0	3.6

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 75 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 101				HRV_5.2 N = 101				HRV_5.8 N = 102				Pooled HRV groups N = 304				Placebo N = 101			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Urinary system (1300)	Urinary tract infection (0628)	0	0	0	3.6	0	0	0	3.6	2	2	0.2	6.9	2	0.7	0.1	2.4	0	0	0	3.6
Vision (431)	Blepharitis (1007)	0	0	0	3.6	0	0	0	3.6	1	1	0	5.3	1	0.3	0	1.8	0	0	0	3.6
	Conjunctivitis (0238)	4	4	1.1	9.8	5	5	1.6	11.2	6	5.9	2.2	12.4	15	4.9	2.8	8	4	4	1.1	9.8

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 76: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 243				HRV_5.2 N = 243				HRV_5.8 N = 244				Pooled HRV groups N = 730				Placebo N = 242			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		115	47.3	40.9	53.8	110	45.3	38.9	51.8	95	38.9	32.8	45.4	320	43.8	40.2	47.5	102	42.1	35.9	48.6
Application site (1820)	Dermatitis contact (0049)	0	0	0	1.5	1	0.4	0	2.3	0	0	0	1.5	1	0.1	0	0.8	1	0.4	0	2.3
	Injection site reaction (0058)	0	0	0	1.5	0	0	0	1.5	1	0.4	0	2.3	1	0.1	0	0.8	0	0	0	1.5
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	2	0.8	0.1	3
	Allergy (1058)	0	0	0	1.5	0	0	0	1.5	1	0.4	0	2.3	1	0.1	0	0.8	0	0	0	1.5
	Injury (9001)	2	0.8	0.1	2.9	0	0	0	1.5	0	0	0	1.5	2	0.3	0	1	0	0	0	1.5
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	1.5	1	0.4	0	2.3	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Fever convulsions (1357)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Spasm generalized (0149)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	1	0.4	0	2.3
Gastrointestinal system (600)	Abdominal pain (0268)	4	1.6	0.5	4.2	4	1.6	0.5	4.2	2	0.8	0.1	2.9	10	1.4	0.7	2.5	2	0.8	0.1	3
	Anus disorder (0269)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Constipation (0204)	0	0	0	1.5	1	0.4	0	2.3	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Stomatitis (0327)	0	0	0	1.5	1	0.4	0	2.3	1	0.4	0	2.3	2	0.3	0	1	0	0	0	1.5
	Stomatitis aphthous (0751)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	1	0.4	0	2.3
Resistance mechanism (1830)	Abscess (0887)	0	0	0	1.5	1	0.4	0	2.3	1	0.4	0	2.3	2	0.3	0	1	0	0	0	1.5
	Infection (0736)	16	6.6	3.8	10.5	14	5.8	3.2	9.5	8	3.3	1.4	6.4	38	5.2	3.7	7.1	9	3.7	1.7	6.9
	Infection bacterial (0738)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	1	0.4	0	2.3
	Infection viral (0740)	72	29.6	24	35.8	61	25.1	19.8	31	61	25	19.7	30.9	194	26.6	23.4	29.9	69	28.5	22.9	34.6
	Moniliasis (0741)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Otitis media (0750)	5	2.1	0.7	4.7	5	2.1	0.7	4.7	1	0.4	0	2.3	11	1.5	0.8	2.7	8	3.3	1.4	6.4

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 76 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 243				HRV_5.2 N = 243				HRV_5.8 N = 244				Pooled HRV groups N = 730				Placebo N = 242			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Respiratory system (1100)	Atelectasis (1197)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	1	0.4	0	2.3
	Bronchitis (0805)	8	3.3	1.4	6.4	15	6.2	3.5	10	11	4.5	2.3	7.9	34	4.7	3.2	6.4	10	4.1	2	7.5
	Bronchospasm (0511)	13	5.3	2.9	9	9	3.7	1.7	6.9	12	4.9	2.6	8.4	34	4.7	3.2	6.4	7	2.9	1.2	5.9
	Laryngitis (0521)	0	0	0	1.5	1	0.4	0	2.3	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Pharyngitis (0523)	4	1.6	0.5	4.2	2	0.8	0.1	2.9	1	0.4	0	2.3	7	1	0.4	2	4	1.7	0.5	4.2
	Pneumonia (0528)	6	2.5	0.9	5.3	11	4.5	2.3	8	12	4.9	2.6	8.4	29	4	2.7	5.7	9	3.7	1.7	6.9
	Rhinitis (0539)	1	0.4	0	2.3	0	0	0	1.5	1	0.4	0	2.3	2	0.3	0	1	0	0	0	1.5
Secondary term (2000)	Varicella (1516)	1	0.4	0	2.3	0	0	0	1.5	1	0.4	0	2.3	2	0.3	0	1	0	0	0	1.5
Skin and appendages (100)	Dermatitis (0007)	0	0	0	1.5	0	0	0	1.5	1	0.4	0	2.3	1	0.1	0	0.8	0	0	0	1.5
	Dermatitis fungal (0009)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
	Rash pustular (0032)	0	0	0	1.5	1	0.4	0	2.3	1	0.4	0	2.3	2	0.3	0	1	2	0.8	0.1	3
Urinary system (1300)	Urinary tract infection (0628)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	2	0.8	0.1	3
Vision (431)	Conjunctivitis (0238)	6	2.5	0.9	5.3	4	1.6	0.5	4.2	0	0	0	1.5	10	1.4	0.7	2.5	3	1.2	0.3	3.6

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 77: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 381				HRV_5.2 D = 379				HRV_5.8 D = 386				Pooled HRV groups D = 1146				Placebo D = 385			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		217	57	51.8	62	220	58	52.9	63.1	201	52.1	47	57.2	638	55.7	52.7	58.6	216	56.1	51	61.1
Application site (1820)	Injection site reaction (0058)	7	1.8	0.7	3.7	5	1.3	0.4	3.1	4	1	0.3	2.6	16	1.4	0.8	2.3	8	2.1	0.9	4.1
	Otitis externa (0059)	0	0	0	1	0	0	0	1	1	0.3	0	1.4	1	0.1	0	0.5	0	0	0	1
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	1	0.3	0	1.4
	Allergic reaction (0712)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
	Allergy (1058)	3	0.8	0.2	2.3	14	3.7	2	6.1	5	1.3	0.4	3	22	1.9	1.2	2.9	9	2.3	1.1	4.4
	Fever (0725)	34	8.9	6.3	12.2	27	7.1	4.7	10.2	36	9.3	6.6	12.7	97	8.5	6.9	10.2	24	6.2	4	9.1
	Injury (9001)	2	0.5	0.1	1.9	0	0	0	1	0	0	0	1	2	0.2	0	0.6	0	0	0	1
	Pallor (0220)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Cardiovascular general (1010)	Cyanosis (0501)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
Fetal (1500)	Vascular malformation peripheral (0764)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 77 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 381				HRV_5.2 D = 379				HRV_5.8 D = 386				Pooled HRV groups D = 1146				Placebo D = 385			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Gastrointestinal system (600)	Abdominal pain (0268)	1	0.3	0	1.5	1	0.3	0	1.5	1	0.3	0	1.4	3	0.3	0.1	0.8	1	0.3	0	1.4
	Anorexia (0165)	4	1	0.3	2.7	5	1.3	0.4	3.1	2	0.5	0.1	1.9	11	1	0.5	1.7	5	1.3	0.4	3
	Constipation (0204)	3	0.8	0.2	2.3	0	0	0	1	2	0.5	0.1	1.9	5	0.4	0.1	1	4	1	0.3	2.6
	Gastroenteritis (0293)	3	0.8	0.2	2.3	5	1.3	0.4	3.1	1	0.3	0	1.4	9	0.8	0.4	1.5	4	1	0.3	2.6
	Gastroesophageal reflux (1149)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Gastrointestinal disorder nos (1262)	0	0	0	1	0	0	0	1	1	0.3	0	1.4	1	0.1	0	0.5	1	0.3	0	1.4
	Stomatitis (0327)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
	Vomiting (0228)	3	0.8	0.2	2.3	4	1.1	0.3	2.7	5	1.3	0.4	3	12	1	0.5	1.8	8	2.1	0.9	4.1
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Earache (0260)	2	0.5	0.1	1.9	1	0.3	0	1.5	1	0.3	0	1.4	4	0.3	0.1	0.9	2	0.5	0.1	1.9
Neoplasm (1700)	Neoplasm nos (1259)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
Psychiatric (500)	Nervousness (0188)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Red blood cell (1210)	Anemia (0544)	1	0.3	0	1.5	0	0	0	1	0	0	0	1	1	0.1	0	0.5	0	0	0	1
Reproductive female (1420)	Leukorrhea (0654)	0	0	0	1	0	0	0	1	1	0.3	0	1.4	1	0.1	0	0.5	0	0	0	1

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 77 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 381				HRV_5.2 D = 379				HRV_5.8 D = 386				Pooled HRV groups D = 1146				Placebo D = 385			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Resistance mechanism (1830)	Abscess (0887)	1	0.3	0	1.5	1	0.3	0	1.5	2	0.5	0.1	1.9	4	0.3	0.1	0.9	0	0	0	1
	Infection (0736)	10	2.6	1.3	4.8	9	2.4	1.1	4.5	10	2.6	1.2	4.7	29	2.5	1.7	3.6	15	3.9	2.2	6.3
	Infection bacterial (0738)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Infection viral (0740)	113	29.7	25.1	34.5	115	30.3	25.8	35.2	114	29.5	25	34.4	342	29.8	27.2	32.6	127	33	28.3	37.9
	Moniliasis (0741)	1	0.3	0	1.5	7	1.8	0.7	3.8	2	0.5	0.1	1.9	10	0.9	0.4	1.6	2	0.5	0.1	1.9
	Otitis media (0750)	0	0	0	1	6	1.6	0.6	3.4	2	0.5	0.1	1.9	8	0.7	0.3	1.4	2	0.5	0.1	1.9
	Upper resp tract infection (0543)	21	5.5	3.4	8.3	12	3.2	1.6	5.5	16	4.1	2.4	6.6	49	4.3	3.2	5.6	16	4.2	2.4	6.7
Respiratory system (1100)	Asthma (1367)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Bronchitis (0805)	12	3.1	1.6	5.4	14	3.7	2	6.1	10	2.6	1.2	4.7	36	3.1	2.2	4.3	4	1	0.3	2.6
	Bronchospasm (0511)	1	0.3	0	1.5	0	0	0	1	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Coughing (0513)	27	7.1	4.7	10.1	23	6.1	3.9	9	25	6.5	4.2	9.4	75	6.5	5.2	8.1	16	4.2	2.4	6.7
	Dyspnea (0514)	0	0	0	1	1	0.3	0	1.5	1	0.3	0	1.4	2	0.2	0	0.6	1	0.3	0	1.4
	Laryngitis (0521)	1	0.3	0	1.5	1	0.3	0	1.5	1	0.3	0	1.4	3	0.3	0.1	0.8	0	0	0	1
	Pharyngitis (0523)	3	0.8	0.2	2.3	9	2.4	1.1	4.5	4	1	0.3	2.6	16	1.4	0.8	2.3	4	1	0.3	2.6
	Pneumonia (0528)	4	1	0.3	2.7	4	1.1	0.3	2.7	4	1	0.3	2.6	12	1	0.5	1.8	3	0.8	0.2	2.3
	Respiratory disorder (0536)	0	0	0	1	7	1.8	0.7	3.8	1	0.3	0	1.4	8	0.7	0.3	1.4	2	0.5	0.1	1.9
	Rhinitis (0539)	8	2.1	0.9	4.1	15	4	2.2	6.4	12	3.1	1.6	5.4	35	3.1	2.1	4.2	14	3.6	2	6
	Sputum increased (0541)	3	0.8	0.2	2.3	9	2.4	1.1	4.5	2	0.5	0.1	1.9	14	1.2	0.7	2	3	0.8	0.2	2.3
Secondary term (2000)	Varicella (1516)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 77 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 381				HRV_5.2 D = 379				HRV_5.8 D = 386				Pooled HRV groups D = 1146				Placebo D = 385			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Skin and appendages (100)	Alopecia (0002)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Dermatitis (0007)	1	0.3	0	1.5	3	0.8	0.2	2.3	2	0.5	0.1	1.9	6	0.5	0.2	1.1	0	0	0	1
	Furunculosis (0016)	3	0.8	0.2	2.3	1	0.3	0	1.5	1	0.3	0	1.4	5	0.4	0.1	1	0	0	0	1
	Pruritus (0024)	0	0	0	1	3	0.8	0.2	2.3	2	0.5	0.1	1.9	5	0.4	0.1	1	0	0	0	1
	Rash (0027)	1	0.3	0	1.5	1	0.3	0	1.5	0	0	0	1	2	0.2	0	0.6	0	0	0	1
	Rash erythematous (0028)	2	0.5	0.1	1.9	0	0	0	1	0	0	0	1	2	0.2	0	0.6	1	0.3	0	1.4
	Rash maculo-papular (0030)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Rash pustular (0032)	0	0	0	1	1	0.3	0	1.5	2	0.5	0.1	1.9	3	0.3	0.1	0.8	0	0	0	1
	Seborrhea (0033)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Skin disorder (0037)	6	1.6	0.6	3.4	8	2.1	0.9	4.1	10	2.6	1.2	4.7	24	2.1	1.3	3.1	10	2.6	1.3	4.7
	Sweat gland disorder (1166)	0	0	0	1	0	0	0	1	1	0.3	0	1.4	1	0.1	0	0.5	0	0	0	1
Urinary system (1300)	Dysuria (0601)	0	0	0	1	1	0.3	0	1.5	2	0.5	0.1	1.9	3	0.3	0.1	0.8	0	0	0	1
Vision (431)	Blepharitis (1007)	1	0.3	0	1.5	0	0	0	1	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Conjunctivitis (0238)	3	0.8	0.2	2.3	4	1.1	0.3	2.7	3	0.8	0.2	2.3	10	0.9	0.4	1.6	3	0.8	0.2	2.3
White cell and reticuloendothelial system (1220)	Lymphadenopathy cervical (0578)	0	0	0	1	0	0	0	1	1	0.3	0	1.4	1	0.1	0	0.5	0	0	0	1

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 78: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 189				HRV_5.2 D = 196				HRV_5.8 D = 192				Pooled HRV groups D = 577				Placebo D = 198			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		131	69.3	62.2	75.8	147	75	68.3	80.9	144	75	68.3	81	422	73.1	69.3	76.7	139	70.2	63.3	76.5
Application site (1820)	Dermatitis contact (0049)	4	2.1	0.6	5.3	7	3.6	1.4	7.2	4	2.1	0.6	5.2	15	2.6	1.5	4.3	6	3	1.1	6.5
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	1.9	1	0.5	0	2.8	1	0.5	0	2.9	2	0.3	0	1.2	0	0	0	1.8
	Death, nos (0722)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.9	1	0.2	0	1	0	0	0	1.8
	Edema generalised (0400)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Fever (0725)	11	5.8	2.9	10.2	19	9.7	5.9	14.7	11	5.7	2.9	10	41	7.1	5.1	9.5	19	9.6	5.9	14.6
	Injury (9001)	1	0.5	0	2.9	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Fever convulsions (1357)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.9	1	0.2	0	1	0	0	0	1.8
Gastrointestinal system (600)	Abdominal pain (0268)	30	15.9	11	21.9	26	13.3	8.9	18.8	27	14.1	9.5	19.8	83	14.4	11.6	17.5	22	11.1	7.1	16.3
	Anorexia (0165)	20	10.6	6.6	15.9	18	9.2	5.5	14.1	13	6.8	3.7	11.3	51	8.8	6.7	11.5	22	11.1	7.1	16.3
	Constipation (0204)	8	4.2	1.8	8.2	11	5.6	2.8	9.8	9	4.7	2.2	8.7	28	4.9	3.2	6.9	2	1	0.1	3.6
	Gastroesophageal reflux (1149)	4	2.1	0.6	5.3	6	3.1	1.1	6.5	7	3.6	1.5	7.4	17	2.9	1.7	4.7	3	1.5	0.3	4.4
	Vomiting (0228)	11	5.8	2.9	10.2	14	7.1	4	11.7	12	6.3	3.3	10.7	37	6.4	4.6	8.7	12	6.1	3.2	10.3
Psychiatric (500)	Nervousness (0188)	39	20.6	15.1	27.1	30	15.3	10.6	21.1	35	18.2	13	24.4	104	18	15	21.4	36	18.2	13.1	24.3
Resistance mechanism (1830)	Infection bacterial (0738)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
	Infection viral (0740)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Moniliasis (0741)	5	2.6	0.9	6.1	5	2.6	0.8	5.9	1	0.5	0	2.9	11	1.9	1	3.4	3	1.5	0.3	4.4
	Otitis media (0750)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Upper resp tract infection (0543)	26	13.8	9.2	19.5	26	13.3	8.9	18.8	33	17.2	12.1	23.3	85	14.7	11.9	17.9	26	13.1	8.8	18.6

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 78 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 189				HRV_5.2 D = 196				HRV_5.8 D = 192				Pooled HRV groups D = 577				Placebo D = 198			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Respiratory system (1100)	Bronchitis (0805)	1	0.5	0	2.9	1	0.5	0	2.8	0	0	0	1.9	2	0.3	0	1.2	0	0	0	1.8
	Coughing (0513)	7	3.7	1.5	7.5	2	1	0.1	3.6	6	3.1	1.2	6.7	15	2.6	1.5	4.3	5	2.5	0.8	5.8
	Laryngitis (0521)	0	0	0	1.9	1	0.5	0	2.8	1	0.5	0	2.9	2	0.3	0	1.2	2	1	0.1	3.6
	Pharyngitis (0523)	68	36	29.1	43.3	89	45.4	38.3	52.7	77	40.1	33.1	47.4	234	40.6	36.5	44.7	77	38.9	32.1	46.1
	Pneumonia (0528)	4	2.1	0.6	5.3	10	5.1	2.5	9.2	4	2.1	0.6	5.2	18	3.1	1.9	4.9	8	4	1.8	7.8
Secondary term (2000)	Varicella (1516)	1	0.5	0	2.9	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	4	2	0.6	5.1
Skin and appendages (100)	Dermatitis (0007)	1	0.5	0	2.9	1	0.5	0	2.8	2	1	0.1	3.7	4	0.7	0.2	1.8	0	0	0	1.8
	Photosensitivity reaction (0022)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Rash erythematous (0028)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
	Rash maculo-papular (0030)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Sweat gland disorder (1166)	1	0.5	0	2.9	1	0.5	0	2.8	1	0.5	0	2.9	3	0.5	0.1	1.5	0	0	0	1.8
Urinary system (1300)	Urinary tract infection (0628)	0	0	0	1.9	0	0	0	1.9	2	1	0.1	3.7	2	0.3	0	1.2	0	0	0	1.8
Vision (431)	Blepharitis (1007)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.9	1	0.2	0	1	0	0	0	1.8
	Conjunctivitis (0238)	4	2.1	0.6	5.3	5	2.6	0.8	5.9	6	3.1	1.2	6.7	15	2.6	1.5	4.3	4	2	0.6	5.1

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 79: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 478				HRV_5.2 D = 474				HRV_5.8 D = 477				Pooled HRV groups D = 1429				Placebo D = 476			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		134	28	24	32.3	128	27	23.1	31.2	115	24.1	20.3	28.2	377	26.4	24.1	28.7	120	25.2	21.4	29.4
Application site (1820)	Dermatitis contact (0049)	0	0	0	0.8	1	0.2	0	1.2	0	0	0	0.8	1	0.1	0	0.4	1	0.2	0	1.2
	Injection site reaction (0058)	0	0	0	0.8	0	0	0	0.8	1	0.2	0	1.2	1	0.1	0	0.4	0	0	0	0.8
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	2	0.4	0.1	1.5
	Allergy (1058)	0	0	0	0.8	0	0	0	0.8	1	0.2	0	1.2	1	0.1	0	0.4	0	0	0	0.8
	Injury (9001)	2	0.4	0.1	1.5	0	0	0	0.8	0	0	0	0.8	2	0.1	0	0.5	0	0	0	0.8
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	0.8	1	0.2	0	1.2	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Fever convulsions (1357)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Spasm generalized (0149)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	1	0.2	0	1.2
Gastrointestinal system (600)	Abdominal pain (0268)	4	0.8	0.2	2.1	4	0.8	0.2	2.1	2	0.4	0.1	1.5	10	0.7	0.3	1.3	2	0.4	0.1	1.5
	Anus disorder (0269)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Constipation (0204)	0	0	0	0.8	1	0.2	0	1.2	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Stomatitis (0327)	0	0	0	0.8	1	0.2	0	1.2	1	0.2	0	1.2	2	0.1	0	0.5	0	0	0	0.8
	Stomatitis aphthous (0751)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	1	0.2	0	1.2

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 79 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 478				HRV_5.2 D = 474				HRV_5.8 D = 477				Pooled HRV groups D = 1429				Placebo D = 476			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Resistance mechanism (1830)	Abscess (0887)	0	0	0	0.8	1	0.2	0	1.2	1	0.2	0	1.2	2	0.1	0	0.5	0	0	0	0.8
	Infection (0736)	17	3.6	2.1	5.6	14	3	1.6	4.9	8	1.7	0.7	3.3	39	2.7	1.9	3.7	9	1.9	0.9	3.6
	Infection bacterial (0738)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	1	0.2	0	1.2
	Infection viral (0740)	81	16.9	13.7	20.6	70	14.8	11.7	18.3	71	14.9	11.8	18.4	222	15.5	13.7	17.5	77	16.2	13	19.8
	Moniliasis (0741)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Otitis media (0750)	5	1	0.3	2.4	5	1.1	0.3	2.4	1	0.2	0	1.2	11	0.8	0.4	1.4	8	1.7	0.7	3.3
Respiratory system (1100)	Atelectasis (1197)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	1	0.2	0	1.2
	Bronchitis (0805)	8	1.7	0.7	3.3	15	3.2	1.8	5.2	11	2.3	1.2	4.1	34	2.4	1.7	3.3	10	2.1	1	3.8
	Bronchospasm (0511)	13	2.7	1.5	4.6	9	1.9	0.9	3.6	12	2.5	1.3	4.4	34	2.4	1.7	3.3	8	1.7	0.7	3.3
	Laryngitis (0521)	0	0	0	0.8	1	0.2	0	1.2	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Pharyngitis (0523)	4	0.8	0.2	2.1	2	0.4	0.1	1.5	1	0.2	0	1.2	7	0.5	0.2	1	4	0.8	0.2	2.1
	Pneumonia (0528)	6	1.3	0.5	2.7	11	2.3	1.2	4.1	13	2.7	1.5	4.6	30	2.1	1.4	3	9	1.9	0.9	3.6
	Rhinitis (0539)	1	0.2	0	1.2	0	0	0	0.8	1	0.2	0	1.2	2	0.1	0	0.5	0	0	0	0.8
Secondary term (2000)	Varicella (1516)	1	0.2	0	1.2	0	0	0	0.8	1	0.2	0	1.2	2	0.1	0	0.5	0	0	0	0.8
Skin and appendages (100)	Dermatitis (0007)	0	0	0	0.8	0	0	0	0.8	1	0.2	0	1.2	1	0.1	0	0.4	0	0	0	0.8
	Dermatitis fungal (0009)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
	Rash pustular (0032)	0	0	0	0.8	1	0.2	0	1.2	1	0.2	0	1.2	2	0.1	0	0.5	2	0.4	0.1	1.5
Urinary system (1300)	Urinary tract infection (0628)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	3	0.6	0.1	1.8
Vision (431)	Conjunctivitis (0238)	6	1.3	0.5	2.7	4	0.8	0.2	2.1	0	0	0	0.8	10	0.7	0.3	1.3	3	0.6	0.1	1.8

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 80: Percentage of subjects with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine y)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 194				HRV_5.2 N = 196				HRV_5.8 N = 194				Pooled HRV groups N = 584				Placebo N = 194			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		2	1	0.1	3.7	0	0	0	1.9	0	0	0	1.9	2	0.3	0	1.2	4	2.1	0.6	5.2
Application site (1820)	Injection site reaction (0058)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Fever (0725)	1	0.5	0	2.8	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Pallor (0220)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Respiratory system (1100)	Bronchitis (0805)	1	0.5	0	2.8	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 81: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 381				HRV_5.2 D = 379				HRV_5.8 D = 386				Pooled HRV groups D = 1146				Placebo D = 385			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		2	0.5	0.1	1.9	0	0	0	1	0	0	0	1	2	0.2	0	0.6	4	1	0.3	2.6
Application site (1820)	Injection site reaction (0058)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
	Fever (0725)	1	0.3	0	1.5	0	0	0	1	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Pallor (0220)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Respiratory system (1100)	Bronchitis (0805)	1	0.3	0	1.5	0	0	0	1	0	0	0	1	1	0.1	0	0.5	0	0	0	1

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 82: Percentage of subjects with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 194				HRV_5.2 N = 196				HRV_5.8 N = 194				Pooled HRV groups N = 584				Placebo N = 194			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		8	4.1	1.8	8	10	5.1	2.5	9.2	6	3.1	1.1	6.6	24	4.1	2.7	6.1	10	5.2	2.5	9.3
Body as a whole general (1810)	Pallor (0220)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
Gastrointestinal system (600)	Gastroenteritis (0293)	3	1.5	0.3	4.5	5	2.6	0.8	5.9	1	0.5	0	2.8	9	1.5	0.7	2.9	4	2.1	0.6	5.2
	Gastrointestinal disorder nos (1262)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.8	1	0.2	0	1	1	0.5	0	2.8
Resistance mechanism (1830)	Infection (0736)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	1	0.5	0	2.8
Respiratory system (1100)	Asthma (1367)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.9
	Bronchitis (0805)	2	1	0.1	3.7	3	1.5	0.3	4.4	0	0	0	1.9	5	0.9	0.3	2	0	0	0	1.9
	Pneumonia (0528)	4	2.1	0.6	5.2	2	1	0.1	3.6	4	2.1	0.6	5.2	10	1.7	0.8	3.1	3	1.5	0.3	4.5

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 83: Percentage of subjects with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 101				HRV_5.2 N = 101				HRV_5.8 N = 102				Pooled HRV groups N = 304				Placebo N = 101			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		6	5.9	2.2	12.5	17	16.8	10.1	25.6	8	7.8	3.4	14.9	31	10.2	7	14.2	5	5	1.6	11.2
Application site (1820)	Dermatitis contact (0049)	0	0	0	3.6	1	1	0	5.4	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	3.6	1	1	0	5.4	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
	Death, nos (0722)	0	0	0	3.6	0	0	0	3.6	1	1	0	5.3	1	0.3	0	1.8	0	0	0	3.6
	Edema generalised (0400)	0	0	0	3.6	0	0	0	3.6	0	0	0	3.6	0	0	0	1.2	1	1	0	5.4
	Fever (0725)	0	0	0	3.6	2	2	0.2	7	1	1	0	5.3	3	1	0.2	2.9	0	0	0	3.6
Central and peripheral nervous system (410)	Fever convulsions (1357)	0	0	0	3.6	0	0	0	3.6	1	1	0	5.3	1	0.3	0	1.8	0	0	0	3.6
Gastrointestinal system (600)	Abdominal pain (0268)	2	2	0.2	7	3	3	0.6	8.4	1	1	0	5.3	6	2	0.7	4.2	0	0	0	3.6
	Anorexia (0165)	1	1	0	5.4	0	0	0	3.6	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
	Constipation (0204)	0	0	0	3.6	1	1	0	5.4	1	1	0	5.3	2	0.7	0.1	2.4	0	0	0	3.6
Psychiatric (500)	Nervousness (0188)	1	1	0	5.4	1	1	0	5.4	1	1	0	5.3	3	1	0.2	2.9	0	0	0	3.6
Resistance mechanism (1830)	Moniliasis (0741)	0	0	0	3.6	1	1	0	5.4	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
Respiratory system (1100)	Bronchitis (0805)	0	0	0	3.6	1	1	0	5.4	0	0	0	3.6	1	0.3	0	1.8	0	0	0	3.6
	Pharyngitis (0523)	3	3	0.6	8.4	7	6.9	2.8	13.8	2	2	0.2	6.9	12	3.9	2.1	6.8	2	2	0.2	7
	Pneumonia (0528)	1	1	0	5.4	6	5.9	2.2	12.5	2	2	0.2	6.9	9	3	1.4	5.5	3	3	0.6	8.4

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 84: Percentage of subjects with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 243				HRV_5.2 N = 243				HRV_5.8 N = 244				Pooled HRV groups N = 730				Placebo N = 242			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	2	0.8	0.1	3
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	1	0.4	0	2.3
Central and peripheral nervous system (410)	Fever convulsions (1357)	1	0.4	0	2.3	0	0	0	1.5	0	0	0	1.5	1	0.1	0	0.8	0	0	0	1.5
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	1.5	0	0	0	1.5	0	0	0	1.5	0	0	0	0.5	1	0.4	0	2.3

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 85: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Brazil (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 381				HRV_5.2 D = 379				HRV_5.8 D = 386				Pooled HRV groups D = 1146				Placebo D = 385			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		8	2.1	0.9	4.1	10	2.6	1.3	4.8	6	1.6	0.6	3.4	24	2.1	1.3	3.1	10	2.6	1.3	4.7
Body as a whole general (1810)	Pallor (0220)	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	0.3	1	0.3	0	1.4
Gastrointestinal system (600)	Gastroenteritis (0293)	3	0.8	0.2	2.3	5	1.3	0.4	3.1	1	0.3	0	1.4	9	0.8	0.4	1.5	4	1	0.3	2.6
	Gastrointestinal disorder nos (1262)	0	0	0	1	0	0	0	1	1	0.3	0	1.4	1	0.1	0	0.5	1	0.3	0	1.4
Resistance mechanism (1830)	Infection (0736)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	1	0.3	0	1.4
Respiratory system (1100)	Asthma (1367)	0	0	0	1	1	0.3	0	1.5	0	0	0	1	1	0.1	0	0.5	0	0	0	1
	Bronchitis (0805)	2	0.5	0.1	1.9	3	0.8	0.2	2.3	0	0	0	1	5	0.4	0.1	1	0	0	0	1
	Pneumonia (0528)	4	1	0.3	2.7	2	0.5	0.1	1.9	4	1	0.3	2.6	10	0.9	0.4	1.6	3	0.8	0.2	2.3

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 86: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Mexico (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 189				HRV_5.2 D = 196				HRV_5.8 D = 192				Pooled HRV groups D = 577				Placebo D = 198			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		6	3.2	1.2	6.8	17	8.7	5.1	13.5	8	4.2	1.8	8	31	5.4	3.7	7.5	6	3	1.1	6.5
Application site (1820)	Dermatitis contact (0049)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
	Death, nos (0722)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.9	1	0.2	0	1	0	0	0	1.8
	Edema generalised (0400)	0	0	0	1.9	0	0	0	1.9	0	0	0	1.9	0	0	0	0.6	1	0.5	0	2.8
	Fever (0725)	0	0	0	1.9	2	1	0.1	3.6	1	0.5	0	2.9	3	0.5	0.1	1.5	0	0	0	1.8
Central and peripheral nervous system (410)	Fever convulsions (1357)	0	0	0	1.9	0	0	0	1.9	1	0.5	0	2.9	1	0.2	0	1	0	0	0	1.8
Gastrointestinal system (600)	Abdominal pain (0268)	2	1.1	0.1	3.8	3	1.5	0.3	4.4	1	0.5	0	2.9	6	1	0.4	2.2	0	0	0	1.8
	Anorexia (0165)	1	0.5	0	2.9	0	0	0	1.9	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
	Constipation (0204)	0	0	0	1.9	1	0.5	0	2.8	1	0.5	0	2.9	2	0.3	0	1.2	0	0	0	1.8
Psychiatric (500)	Nervousness (0188)	1	0.5	0	2.9	1	0.5	0	2.8	1	0.5	0	2.9	3	0.5	0.1	1.5	0	0	0	1.8
Resistance mechanism (1830)	Moniliasis (0741)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
Respiratory system (1100)	Bronchitis (0805)	0	0	0	1.9	1	0.5	0	2.8	0	0	0	1.9	1	0.2	0	1	0	0	0	1.8
	Pharyngitis (0523)	3	1.6	0.3	4.6	7	3.6	1.4	7.2	2	1	0.1	3.7	12	2.1	1.1	3.6	2	1	0.1	3.6
	Pneumonia (0528)	1	0.5	0	2.9	6	3.1	1.1	6.5	2	1	0.1	3.7	9	1.6	0.7	2.9	3	1.5	0.3	4.4

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 87: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from Day 0 to Day 42 after any vaccination in Venezuela (total vaccinated cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 478				HRV_5.2 D = 474				HRV_5.8 D = 477				Pooled HRV groups D = 1429				Placebo D = 476			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	2	0.4	0.1	1.5
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	1	0.2	0	1.2
Central and peripheral nervous system (410)	Fever convulsions (1357)	1	0.2	0	1.2	0	0	0	0.8	0	0	0	0.8	1	0.1	0	0.4	0	0	0	0.8
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.8	0	0	0	0.8	0	0	0	0.8	0	0	0	0.3	1	0.2	0	1.2

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 88: Number and percentage of subjects who received vaccine dose(s) (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Total number of doses received	HRV_4.7 (N = 499)		HRV_5.2 (N = 487)		HRV_5.8 (N = 493)		Placebo (N = 486)		Total (N = 1965)	
	n	%	n	%	n	%	n	%	n	%
0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
1	21	4.2	26	5.3	22	4.5	11	2.3	80	4.1
2	478	95.8	461	94.7	471	95.5	475	97.7	1885	95.9
Any	499	100.0	487	100.0	493	100.0	486	100.0	1965	100.0

Notes: N = number of subjects in each group or in total (sum of all groups)
n/% = number/percentage of subjects receiving the specified total number of doses in each group or in total
Any = number and percentage of subjects receiving at least one dose

Supplement 89: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15 days follow-up period (ATP cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	499	455	91.2	88.3	93.5
	HRV_5.2	487	439	90.1	87.1	92.6
	HRV_5.8	493	450	91.3	88.4	93.6
	Pooled HRV groups	1479	1344	90.9	89.3	92.3
	Placebo	486	452	93.0	90.4	95.1
Dose 2	**HRV_4.7**	478	409	85.6	82.1	88.6
	HRV_5.2	461	404	87.6	84.3	90.5
	HRV_5.8	471	414	87.9	84.6	90.7
	Pooled HRV groups	1410	1227	87.0	85.2	88.7
	Placebo	475	418	88.0	84.7	90.8
Overall/dose	**HRV_4.7**	977	864	88.4	86.3	90.4
	HRV_5.2	948	843	88.9	86.8	90.9
	HRV_5.8	964	864	89.6	87.5	91.5
	Pooled HRV groups	2889	2571	89.0	87.8	90.1
	Placebo	961	870	90.5	88.5	92.3
Overall/subject	**HRV_4.7**	499	476	95.4	93.2	97.1
	HRV_5.2	487	463	95.1	92.8	96.8
	HRV_5.8	493	469	95.1	92.8	96.9
	Pooled HRV groups	1479	1408	95.2	94.0	96.2
	Placebo	486	472	97.1	95.2	98.4

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 90: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period (ATP cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	499	110	22.0	18.5	25.9
	HRV_5.2	487	110	22.6	18.9	26.6
	HRV_5.8	493	125	25.4	21.6	29.4
	Pooled HRV groups	1479	345	23.3	21.2	25.6
	Placebo	486	116	23.9	20.1	27.9
Dose 2	**HRV_4.7**	478	99	20.7	17.2	24.6
	HRV_5.2	461	99	21.5	17.8	25.5
	HRV_5.8	471	99	21.0	17.4	25.0
	Pooled HRV groups	1410	297	21.1	19.0	23.3
	Placebo	475	98	20.6	17.1	24.6
Overall/dose	**HRV_4.7**	977	209	21.4	18.9	24.1
	HRV_5.2	948	209	22.0	19.4	24.8
	HRV_5.8	964	224	23.2	20.6	26.0
	Pooled HRV groups	2889	642	22.2	20.7	23.8
	Placebo	961	214	22.3	19.7	25.0
Overall/subject	**HRV_4.7**	499	170	34.1	29.9	38.4
	HRV_5.2	487	179	36.8	32.5	41.2
	HRV_5.8	493	174	35.3	31.1	39.7
	Pooled HRV groups	1479	523	35.4	32.9	37.9
	Placebo	486	175	36.0	31.7	40.5

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N = number of subjects having received at least one dose
n/% = number/percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 91: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up period (ATP cohort for safety for subset planned to receive two doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	499	245	49.1	44.6	53.6
	HRV_5.2	487	237	48.7	44.1	53.2
	HRV_5.8	493	240	48.7	44.2	53.2
	Pooled HRV groups	1479	722	48.8	46.2	51.4
	Placebo	486	237	48.8	44.2	53.3
Dose 2	**HRV_4.7**	478	194	40.6	36.1	45.1
	HRV_5.2	461	202	43.8	39.2	48.5
	HRV_5.8	471	213	45.2	40.7	49.8
	Pooled HRV groups	1410	609	43.2	40.6	45.8
	Placebo	475	197	41.5	37.0	46.1
Overall/dose	**HRV_4.7**	977	439	44.9	41.8	48.1
	HRV_5.2	948	439	46.3	43.1	49.5
	HRV_5.8	964	453	47.0	43.8	50.2
	Pooled HRV groups	2889	1331	46.1	44.2	47.9
	Placebo	961	434	45.2	42.0	48.4
Overall/subject	**HRV_4.7**	499	251	50.3	45.8	54.8
	HRV_5.2	487	247	50.7	46.2	55.2
	HRV_5.8	493	254	51.5	47.0	56.0
	Pooled HRV groups	1479	752	50.8	48.3	53.4
	Placebo	486	242	49.8	45.3	54.3

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N = number of subjects having received at least one dose
n/% = number/percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92: Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		1											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		499				487				493			
COUGH	Total	299	59.9	55.5	64.2	278	57.1	52.6	61.5	286	58.0	53.5	62.4
	Grade 2*3	160	32.1	28.0	36.4	131	26.9	23.0	31.1	146	29.6	25.6	33.9
	Grade 3	42	8.4	6.1	11.2	44	9.0	6.6	11.9	46	9.3	6.9	12.2
	Related	94	18.8	15.5	22.5	83	17.0	13.8	20.7	78	15.8	12.7	19.3
DIARRHEA	Total	31	6.2	4.3	8.7	27	5.5	3.7	8.0	38	7.7	5.5	10.4
	Grade 2*3	18	3.6	2.2	5.6	20	4.1	2.5	6.3	26	5.3	3.5	7.6
	Grade 3	8	1.6	0.7	3.1	9	1.8	0.8	3.5	10	2.0	1.0	3.7
	Related	14	2.8	1.5	4.7	15	3.1	1.7	5.0	27	5.5	3.6	7.9
IRRITABILITY	Total	353	70.7	66.5	74.7	335	68.8	64.5	72.9	354	71.8	67.6	75.7
	Grade 2*3	233	46.7	42.2	51.2	208	42.7	38.3	47.2	232	47.1	42.6	51.6
	Grade 3	63	12.6	9.8	15.9	62	12.7	9.9	16.0	68	13.8	10.9	17.2
	Related	212	42.5	38.1	47.0	189	38.8	34.5	43.3	212	43.0	38.6	47.5
LOSS OF APPETITE	Total	158	31.7	27.6	35.9	161	33.1	28.9	37.4	156	31.6	27.6	36.0
	Grade 2*3	49	9.8	7.4	12.8	42	8.6	6.3	11.5	62	12.6	9.8	15.8
	Grade 3	6	1.2	0.4	2.6	4	0.8	0.2	2.1	11	2.2	1.1	4.0
	Related	66	13.2	10.4	16.5	67	13.8	10.8	17.1	70	14.2	11.2	17.6
FEVER	Total	306	61.3	56.9	65.6	302	62.0	57.5	66.3	306	62.1	57.6	66.4
	Grade 2*3	113	22.6	19.0	26.6	96	19.7	16.3	23.5	115	23.3	19.7	27.3
	Grade 3	6	1.2	0.4	2.6	6	1.2	0.5	2.7	8	1.6	0.7	3.2
	Related	182	36.5	32.2	40.9	160	32.9	28.7	37.2	172	34.9	30.7	39.3
VOMITING	Total	76	15.2	12.2	18.7	89	18.3	14.9	22.0	75	15.2	12.2	18.7
	Grade 2*3	33	6.6	4.6	9.2	50	10.3	7.7	13.3	33	6.7	4.7	9.3
	Grade 3	12	2.4	1.2	4.2	19	3.9	2.4	6.0	18	3.7	2.2	5.7
	Related	39	7.8	5.6	10.5	36	7.4	5.2	10.1	33	6.7	4.7	9.3

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		1							
		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		1479				486			
COUGH	Total	863	58.4	55.8	60.9	303	62.3	57.9	66.7
	Grade 2*3	437	29.5	27.2	31.9	165	34.0	29.7	38.4
	Grade 3	132	8.9	7.5	10.5	31	6.4	4.4	8.9
	Related	255	17.2	15.3	19.3	87	17.9	14.6	21.6
DIARRHEA	Total	96	6.5	5.3	7.9	38	7.8	5.6	10.6
	Grade 2*3	64	4.3	3.3	5.5	22	4.5	2.9	6.8
	Grade 3	27	1.8	1.2	2.6	7	1.4	0.6	2.9
	Related	56	3.8	2.9	4.9	20	4.1	2.5	6.3
IRRITABILITY	Total	1042	70.5	68.1	72.8	367	75.5	71.4	79.3
	Grade 2*3	673	45.5	42.9	48.1	247	50.8	46.3	55.4
	Grade 3	193	13.0	11.4	14.9	77	15.8	12.7	19.4
	Related	613	41.4	38.9	44.0	208	42.8	38.4	47.3
LOSS OF APPETITE	Total	475	32.1	29.7	34.6	169	34.8	30.5	39.2
	Grade 2*3	153	10.3	8.8	12.0	57	11.7	9.0	14.9
	Grade 3	21	1.4	0.9	2.2	8	1.6	0.7	3.2
	Related	203	13.7	12.0	15.6	72	14.8	11.8	18.3
FEVER	Total	914	61.8	59.3	64.3	309	63.6	59.1	67.9
	Grade 2*3	324	21.9	19.8	24.1	107	22.0	18.4	26.0
	Grade 3	20	1.4	0.8	2.1	10	2.1	1.0	3.8
	Related	514	34.8	32.3	37.2	163	33.5	29.3	37.9
VOMITING	Total	240	16.2	14.4	18.2	73	15.0	12.0	18.5
	Grade 2*3	116	7.8	6.5	9.3	34	7.0	4.9	9.6
	Grade 3	49	3.3	2.5	4.4	9	1.9	0.9	3.5
	Related	108	7.3	6.0	8.7	43	8.8	6.5	11.7

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Dose		2											
Group		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		478				461				471			
COUGH	Total	291	60.9	56.3	65.3	291	63.1	58.5	67.5	305	64.8	60.3	69.1
	Grade 2*3	158	33.1	28.8	37.5	150	32.5	28.3	37.0	164	34.8	30.5	39.3
	Grade 3	48	10.0	7.5	13.1	48	10.4	7.8	13.6	49	10.4	7.8	13.5
	Related	85	17.8	14.5	21.5	97	21.0	17.4	25.1	95	20.2	16.6	24.1
DIARRHEA	Total	36	7.5	5.3	10.3	32	6.9	4.8	9.7	41	8.7	6.3	11.6
	Grade 2*3	28	5.9	3.9	8.4	21	4.6	2.8	6.9	27	5.7	3.8	8.2
	Grade 3	7	1.5	0.6	3.0	10	2.2	1.0	4.0	13	2.8	1.5	4.7
	Related	17	3.6	2.1	5.6	22	4.8	3.0	7.1	19	4.0	2.4	6.2
IRRITABILITY	Total	276	57.7	53.2	62.2	274	59.4	54.8	64.0	287	60.9	56.4	65.4
	Grade 2*3	153	32.0	27.8	36.4	151	32.8	28.5	37.2	174	36.9	32.6	41.5
	Grade 3	50	10.5	7.9	13.6	39	8.5	6.1	11.4	44	9.3	6.9	12.3
	Related	155	32.4	28.2	36.8	148	32.1	27.9	36.6	158	33.5	29.3	38.0
LOSS OF APPETITE	Total	139	29.1	25.0	33.4	135	29.3	25.2	33.7	137	29.1	25.0	33.4
	Grade 2*3	63	13.2	10.3	16.5	58	12.6	9.7	16.0	57	12.1	9.3	15.4
	Grade 3	13	2.7	1.5	4.6	16	3.5	2.0	5.6	4	0.8	0.2	2.2
	Related	51	10.7	8.0	13.8	48	10.4	7.8	13.6	46	9.8	7.2	12.8
FEVER	Total	257	53.8	49.2	58.3	244	52.9	48.3	57.6	260	55.2	50.6	59.8
	Grade 2*3	98	20.5	17.0	24.4	102	22.1	18.4	26.2	103	21.9	18.2	25.9
	Grade 3	7	1.5	0.6	3.0	11	2.4	1.2	4.2	14	3.0	1.6	4.9
	Related	123	25.7	21.9	29.9	109	23.6	19.8	27.8	131	27.8	23.8	32.1
VOMITING	Total	51	10.7	8.0	13.8	54	11.7	8.9	15.0	56	11.9	9.1	15.2
	Grade 2*3	24	5.0	3.2	7.4	31	6.7	4.6	9.4	28	5.9	4.0	8.5
	Grade 3	12	2.5	1.3	4.3	17	3.7	2.2	5.8	14	3.0	1.6	4.9
	Related	28	5.9	3.9	8.4	25	5.4	3.5	7.9	21	4.5	2.8	6.7

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		2							
		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		1410				475			
COUGH	Total	887	62.9	60.3	65.4	298	62.7	58.2	67.1
	Grade 2*3	472	33.5	31.0	36.0	175	36.8	32.5	41.4
	Grade 3	145	10.3	8.7	12.0	44	9.3	6.8	12.2
	Related	277	19.6	17.6	21.8	93	19.6	16.1	23.4
DIARRHEA	Total	109	7.7	6.4	9.2	42	8.8	6.4	11.8
	Grade 2*3	76	5.4	4.3	6.7	30	6.3	4.3	8.9
	Grade 3	30	2.1	1.4	3.0	13	2.7	1.5	4.6
	Related	58	4.1	3.1	5.3	20	4.2	2.6	6.4
IRRITABILITY	Total	837	59.4	56.7	61.9	278	58.5	53.9	63.0
	Grade 2*3	478	33.9	31.4	36.4	165	34.7	30.5	39.2
	Grade 3	133	9.4	8.0	11.1	38	8.0	5.7	10.8
	Related	461	32.7	30.2	35.2	145	30.5	26.4	34.9
LOSS OF APPETITE	Total	411	29.1	26.8	31.6	134	28.2	24.2	32.5
	Grade 2*3	178	12.6	10.9	14.5	62	13.1	10.2	16.4
	Grade 3	33	2.3	1.6	3.3	11	2.3	1.2	4.1
	Related	145	10.3	8.7	12.0	50	10.5	7.9	13.6
FEVER	Total	761	54.0	51.3	56.6	268	56.4	51.8	60.9
	Grade 2*3	303	21.5	19.4	23.7	87	18.3	14.9	22.1
	Grade 3	32	2.3	1.6	3.2	11	2.3	1.2	4.1
	Related	363	25.7	23.5	28.1	113	23.8	20.0	27.9
VOMITING	Total	161	11.4	9.8	13.2	53	11.2	8.5	14.3
	Grade 2*3	83	5.9	4.7	7.2	26	5.5	3.6	7.9
	Grade 3	43	3.0	2.2	4.1	14	2.9	1.6	4.9
	Related	74	5.2	4.1	6.5	20	4.2	2.6	6.4

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Dose		Overall/Dose											
Group		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		977				948				964			
COUGH	Total	590	60.4	57.2	63.5	569	60.0	56.8	63.2	591	61.3	58.1	64.4
	Grade 2*3	318	32.5	29.6	35.6	281	29.6	26.7	32.7	310	32.2	29.2	35.2
	Grade 3	90	9.2	7.5	11.2	92	9.7	7.9	11.8	95	9.9	8.0	11.9
	Related	179	18.3	15.9	20.9	180	19.0	16.5	21.6	173	17.9	15.6	20.5
DIARRHEA	Total	67	6.9	5.4	8.6	59	6.2	4.8	8.0	79	8.2	6.5	10.1
	Grade 2*3	46	4.7	3.5	6.2	41	4.3	3.1	5.8	53	5.5	4.1	7.1
	Grade 3	15	1.5	0.9	2.5	19	2.0	1.2	3.1	23	2.4	1.5	3.6
	Related	31	3.2	2.2	4.5	37	3.9	2.8	5.3	46	4.8	3.5	6.3
IRRITABILITY	Total	629	64.4	61.3	67.4	609	64.2	61.1	67.3	641	66.5	63.4	69.5
	Grade 2*3	386	39.5	36.4	42.7	359	37.9	34.8	41.0	406	42.1	39.0	45.3
	Grade 3	113	11.6	9.6	13.7	101	10.7	8.8	12.8	112	11.6	9.7	13.8
	Related	367	37.6	34.5	40.7	337	35.5	32.5	38.7	370	38.4	35.3	41.5
LOSS OF APPETITE	Total	297	30.4	27.5	33.4	296	31.2	28.3	34.3	293	30.4	27.5	33.4
	Grade 2*3	112	11.5	9.5	13.6	100	10.5	8.7	12.7	119	12.3	10.3	14.6
	Grade 3	19	1.9	1.2	3.0	20	2.1	1.3	3.2	15	1.6	0.9	2.6
	Related	117	12.0	10.0	14.2	115	12.1	10.1	14.4	116	12.0	10.0	14.3
FEVER	Total	563	57.6	54.5	60.7	546	57.6	54.4	60.8	566	58.7	55.5	61.8
	Grade 2*3	211	21.6	19.1	24.3	198	20.9	18.3	23.6	218	22.6	20.0	25.4
	Grade 3	13	1.3	0.7	2.3	17	1.8	1.0	2.9	22	2.3	1.4	3.4
	Related	305	31.2	28.3	34.2	269	28.4	25.5	31.4	303	31.4	28.5	34.5
VOMITING	Total	127	13.0	11.0	15.3	143	15.1	12.9	17.5	131	13.6	11.5	15.9
	Grade 2*3	57	5.8	4.4	7.5	81	8.5	6.8	10.5	61	6.3	4.9	8.1
	Grade 3	24	2.5	1.6	3.6	36	3.8	2.7	5.2	32	3.3	2.3	4.7
	Related	67	6.9	5.4	8.6	61	6.4	5.0	8.2	54	5.6	4.2	7.2

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

		Overall/Dose							
Group		**Pooled HRV groups**				**Placebo**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
N		2889				961			
COUGH	**Total**	1750	60.6	58.8	62.4	601	62.5	59.4	65.6
	Grade 2*3	909	31.5	29.8	33.2	340	35.4	32.4	38.5
	Grade 3	277	9.6	8.5	10.7	75	7.8	6.2	9.7
	Related	532	18.4	17.0	19.9	180	18.7	16.3	21.3
DIARRHEA	**Total**	205	7.1	6.2	8.1	80	8.3	6.7	10.3
	Grade 2*3	140	4.8	4.1	5.7	52	5.4	4.1	7.0
	Grade 3	57	2.0	1.5	2.5	20	2.1	1.3	3.2
	Related	114	3.9	3.3	4.7	40	4.2	3.0	5.6
IRRITABILITY	**Total**	1879	65.0	63.3	66.8	645	67.1	64.0	70.1
	Grade 2*3	1151	39.8	38.0	41.7	412	42.9	39.7	46.1
	Grade 3	326	11.3	10.2	12.5	115	12.0	10.0	14.2
	Related	1074	37.2	35.4	39.0	353	36.7	33.7	39.9
LOSS OF APPETITE	**Total**	886	30.7	29.0	32.4	303	31.5	28.6	34.6
	Grade 2*3	331	11.5	10.3	12.7	119	12.4	10.4	14.6
	Grade 3	54	1.9	1.4	2.4	19	2.0	1.2	3.1
	Related	348	12.0	10.9	13.3	122	12.7	10.7	15.0
FEVER	**Total**	1675	58.0	56.2	59.8	577	60.0	56.9	63.2
	Grade 2*3	627	21.7	20.2	23.3	194	20.2	17.7	22.9
	Grade 3	52	1.8	1.3	2.4	21	2.2	1.4	3.3
	Related	877	30.4	28.7	32.1	276	28.7	25.9	31.7
VOMITING	**Total**	401	13.9	12.6	15.2	126	13.1	11.0	15.4
	Grade 2*3	199	6.9	6.0	7.9	60	6.2	4.8	8.0
	Grade 3	92	3.2	2.6	3.9	23	2.4	1.5	3.6
	Related	182	6.3	5.4	7.2	63	6.6	5.1	8.3

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

Dose Group		Overall/Subject											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		499				487				493			
COUGH	Total	388	77.8	73.8	81.3	377	77.4	73.4	81.1	383	77.7	73.8	81.3
	Grade 2*3	235	47.1	42.6	51.6	224	46.0	41.5	50.5	234	47.5	43.0	52.0
	Grade 3	82	16.4	13.3	20.0	82	16.8	13.6	20.5	80	16.2	13.1	19.8
	Related	135	27.1	23.2	31.2	144	29.6	25.5	33.8	142	28.8	24.8	33.0
DIARRHEA	Total	64	12.8	10.0	16.1	53	10.9	8.3	14.0	68	13.8	10.9	17.2
	Grade 2*3	44	8.8	6.5	11.7	39	8.0	5.8	10.8	48	9.7	7.3	12.7
	Grade 3	15	3.0	1.7	4.9	19	3.9	2.4	6.0	22	4.5	2.8	6.7
	Related	31	6.2	4.3	8.7	35	7.2	5.1	9.9	41	8.3	6.0	11.1
IRRITABILITY	Total	390	78.2	74.3	81.7	389	79.9	76.0	83.3	401	81.3	77.6	84.7
	Grade 2*3	283	56.7	52.2	61.1	270	55.4	50.9	59.9	286	58.0	53.5	62.4
	Grade 3	92	18.4	15.1	22.1	88	18.1	14.8	21.8	87	17.6	14.4	21.3
	Related	228	45.7	41.3	50.2	212	43.5	39.1	48.1	236	47.9	43.4	52.4
LOSS OF APPETITE	Total	224	44.9	40.5	49.4	223	45.8	41.3	50.3	215	43.6	39.2	48.1
	Grade 2*3	98	19.6	16.2	23.4	86	17.7	14.4	21.3	100	20.3	16.8	24.1
	Grade 3	17	3.4	2.0	5.4	18	3.7	2.2	5.8	15	3.0	1.7	5.0
	Related	97	19.4	16.1	23.2	92	18.9	15.5	22.7	92	18.7	15.3	22.4
FEVER	Total	380	76.2	72.2	79.8	376	77.2	73.2	80.9	372	75.5	71.4	79.2
	Grade 2*3	175	35.1	30.9	39.4	169	34.7	30.5	39.1	179	36.3	32.1	40.7
	Grade 3	13	2.6	1.4	4.4	17	3.5	2.0	5.5	21	4.3	2.7	6.4
	Related	209	41.9	37.5	46.4	188	38.6	34.3	43.1	203	41.2	36.8	45.7
VOMITING	Total	107	21.4	17.9	25.3	125	25.7	21.8	29.8	113	22.9	19.3	26.9
	Grade 2*3	49	9.8	7.4	12.8	73	15.0	11.9	18.5	57	11.6	8.9	14.7
	Grade 3	23	4.6	2.9	6.8	35	7.2	5.1	9.9	30	6.1	4.1	8.6
	Related	55	11.0	8.4	14.1	56	11.5	8.8	14.7	48	9.7	7.3	12.7

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 92 (continued): Percentage of doses and subjects reporting each solicited general symptoms included those graded "3" and those graded "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15-day follow-up (ATP cohort for safety for subset planned to receive two doses of study vaccine)

		Overall/Subject							
Group		**Pooled HRV groups**				**Placebo**			
		n	**%**	**95% CI**		**n**	**%**	**95% CI**	
				LL	**UL**			**LL**	**UL**
N		1479				486			
COUGH	**Total**	1148	77.6	75.4	79.7	389	80.0	76.2	83.5
	Grade 2*3	693	46.9	44.3	49.4	260	53.5	49.0	58.0
	Grade 3	244	16.5	14.6	18.5	68	14.0	11.0	17.4
	Related	421	28.5	26.2	30.8	139	28.6	24.6	32.8
DIARRHEA	**Total**	185	12.5	10.9	14.3	74	15.2	12.1	18.7
	Grade 2*3	131	8.9	7.5	10.4	50	10.3	7.7	13.3
	Grade 3	56	3.8	2.9	4.9	18	3.7	2.2	5.8
	Related	107	7.2	6.0	8.7	38	7.8	5.6	10.6
IRRITABILITY	**Total**	1180	79.8	77.6	81.8	401	82.5	78.8	85.8
	Grade 2*3	839	56.7	54.2	59.3	300	61.7	57.2	66.1
	Grade 3	267	18.1	16.1	20.1	103	21.2	17.6	25.1
	Related	676	45.7	43.1	48.3	222	45.7	41.2	50.2
LOSS OF APPETITE	**Total**	662	44.8	42.2	47.3	226	46.5	42.0	51.0
	Grade 2*3	284	19.2	17.2	21.3	100	20.6	17.1	24.4
	Grade 3	50	3.4	2.5	4.4	19	3.9	2.4	6.0
	Related	281	19.0	17.0	21.1	97	20.0	16.5	23.8
FEVER	**Total**	1128	76.3	74.0	78.4	384	79.0	75.1	82.5
	Grade 2*3	523	35.4	32.9	37.9	160	32.9	28.8	37.3
	Grade 3	51	3.4	2.6	4.5	20	4.1	2.5	6.3
	Related	600	40.6	38.1	43.1	193	39.7	35.3	44.2
VOMITING	**Total**	345	23.3	21.2	25.6	110	22.6	19.0	26.6
	Grade 2*3	179	12.1	10.5	13.9	54	11.1	8.5	14.2
	Grade 3	88	5.9	4.8	7.3	22	4.5	2.9	6.8
	Related	159	10.8	9.2	12.4	56	11.5	8.8	14.7

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting the specified symptom for a considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 93: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		322	64.5	60.2	68.7	309	63.4	59	67.7	296	60	55.6	64.4	927	62.7	60.2	65.1	304	62.6	58.1	66.9
Application site (1820)	Dermatitis contact (0049)	4	0.8	0.2	2	8	1.6	0.7	3.2	3	0.6	0.1	1.8	15	1	0.6	1.7	6	1.2	0.5	2.7
	Injection site reaction (0058)	7	1.4	0.6	2.9	4	0.8	0.2	2.1	5	1	0.3	2.4	16	1.1	0.6	1.8	5	1	0.3	2.4
	Otitis externa (0059)	0	0	0	0.7	0	0	0	0.8	1	0.2	0	1.1	1	0.1	0	0.4	0	0	0	0.8
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.7	2	0.4	0	1.5	1	0.2	0	1.1	3	0.2	0	0.6	1	0.2	0	1.1
	Allergic reaction (0712)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	3	0.6	0.1	1.8
	Allergy (1058)	3	0.6	0.1	1.7	6	1.2	0.5	2.7	5	1	0.3	2.4	14	0.9	0.5	1.6	8	1.6	0.7	3.2
	Death, nos (0722)	0	0	0	0.7	0	0	0	0.8	1	0.2	0	1.1	1	0.1	0	0.4	0	0	0	0.8
	Fever (0725)	40	8	5.8	10.8	36	7.4	5.2	10.1	40	8.1	5.9	10.9	116	7.8	6.5	9.3	32	6.6	4.5	9.2
	Injury (9001)	4	0.8	0.2	2	0	0	0	0.8	0	0	0	0.7	4	0.3	0.1	0.7	0	0	0	0.8
Cardiovascular general (1010)	Cyanosis (0501)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	0.7	2	0.4	0	1.5	0	0	0	0.7	2	0.1	0	0.5	1	0.2	0	1.1
	Fever convulsions (1357)	1	0.2	0	1.1	0	0	0	0.8	1	0.2	0	1.1	2	0.1	0	0.5	0	0	0	0.8
	Spasm generalized (0149)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 93 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
	Vascular malformation peripheral (0764)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
Gastrointestinal system (600)	Abdominal pain (0268)	30	6	4.1	8.5	25	5.1	3.3	7.5	23	4.7	3	6.9	78	5.3	4.2	6.5	22	4.5	2.9	6.8
	Anorexia (0165)	18	3.6	2.2	5.6	17	3.5	2	5.5	12	2.4	1.3	4.2	47	3.2	2.3	4.2	21	4.3	2.7	6.5
	Anus disorder (0269)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Constipation (0204)	10	2	1	3.7	10	2.1	1	3.7	9	1.8	0.8	3.4	29	2	1.3	2.8	5	1	0.3	2.4
	Gastroenteritis (0293)	2	0.4	0	1.4	5	1	0.3	2.4	1	0.2	0	1.1	8	0.5	0.2	1.1	2	0.4	0	1.5
	Gastroesophageal reflux (1149)	4	0.8	0.2	2	6	1.2	0.5	2.7	7	1.4	0.6	2.9	17	1.1	0.7	1.8	3	0.6	0.1	1.8
	Gastrointestinal disorder nos (1262)	0	0	0	0.7	0	0	0	0.8	1	0.2	0	1.1	1	0.1	0	0.4	0	0	0	0.8
	Stomatitis (0327)	0	0	0	0.7	1	0.2	0	1.1	1	0.2	0	1.1	2	0.1	0	0.5	1	0.2	0	1.1
	Stomatitis aphthous (0751)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
	Vomiting (0228)	13	2.6	1.4	4.4	16	3.3	1.9	5.3	12	2.4	1.3	4.2	41	2.8	2	3.7	18	3.7	2.2	5.8
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Earache (0260)	2	0.4	0	1.4	1	0.2	0	1.1	1	0.2	0	1.1	4	0.3	0.1	0.7	1	0.2	0	1.1
Neoplasm (1700)	Neoplasm nos (1259)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
Psychiatric (500)	Nervousness (0188)	26	5.2	3.4	7.5	22	4.5	2.9	6.8	26	5.3	3.5	7.6	74	5	3.9	6.2	32	6.6	4.5	9.2

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 93 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Red blood cell (1210)	Anemia (0544)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
Resistance mechanism (1830)	Abscess (0887)	1	0.2	0	1.1	1	0.2	0	1.1	3	0.6	0.1	1.8	5	0.3	0.1	0.8	0	0	0	0.8
	Infection (0736)	26	5.2	3.4	7.5	19	3.9	2.4	6	17	3.4	2	5.5	62	4.2	3.2	5.3	20	4.1	2.5	6.3
	Infection bacterial (0738)	1	0.2	0	1.1	2	0.4	0	1.5	0	0	0	0.7	3	0.2	0	0.6	1	0.2	0	1.1
	Infection viral (0740)	159	31.9	27.8	36.2	142	29.2	25.2	33.4	144	29.2	25.2	33.4	445	30.1	27.8	32.5	151	31.1	27	35.4
	Moniliasis (0741)	7	1.4	0.6	2.9	10	2.1	1	3.7	3	0.6	0.1	1.8	20	1.4	0.8	2.1	4	0.8	0.2	2.1
	Otitis media (0750)	5	1	0.3	2.3	11	2.3	1.1	4	3	0.6	0.1	1.8	19	1.3	0.8	2	9	1.9	0.9	3.5
	Upper resp tract infection (0543)	39	7.8	5.6	10.5	32	6.6	4.5	9.1	40	8.1	5.9	10.9	111	7.5	6.2	9	37	7.6	5.4	10.3
Respiratory system (1100)	Asthma (1367)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Atelectasis (1197)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
	Bronchitis (0805)	19	3.8	2.3	5.9	21	4.3	2.7	6.5	20	4.1	2.5	6.2	60	4.1	3.1	5.2	12	2.5	1.3	4.3
	Bronchospasm (0511)	14	2.8	1.5	4.7	8	1.6	0.7	3.2	11	2.2	1.1	4	33	2.2	1.5	3.1	7	1.4	0.6	2.9
	Coughing (0513)	23	4.6	2.9	6.8	21	4.3	2.7	6.5	25	5.1	3.3	7.4	69	4.7	3.6	5.9	17	3.5	2.1	5.5
	Dyspnea (0514)	0	0	0	0.7	1	0.2	0	1.1	1	0.2	0	1.1	2	0.1	0	0.5	1	0.2	0	1.1
	Laryngitis (0521)	1	0.2	0	1.1	3	0.6	0.1	1.8	1	0.2	0	1.1	5	0.3	0.1	0.8	2	0.4	0	1.5
	Pharyngitis (0523)	52	10.4	7.9	13.4	64	13.1	10.3	16.5	54	11	8.3	14	170	11.5	9.9	13.2	65	13.4	10.5	16.7
	Pneumonia (0528)	13	2.6	1.4	4.4	23	4.7	3	7	19	3.9	2.3	6	55	3.7	2.8	4.8	20	4.1	2.5	6.3
	Respiratory disorder (0536)	0	0	0	0.7	5	1	0.3	2.4	1	0.2	0	1.1	6	0.4	0.1	0.9	2	0.4	0	1.5
	Rhinitis (0539)	7	1.4	0.6	2.9	13	2.7	1.4	4.5	12	2.4	1.3	4.2	32	2.2	1.5	3	11	2.3	1.1	4
	Sputum increased (0541)	3	0.6	0.1	1.7	7	1.4	0.6	2.9	1	0.2	0	1.1	11	0.7	0.4	1.3	3	0.6	0.1	1.8

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 93 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Secondary term (2000)	Varicella (1516)	2	0.4	0	1.4	1	0.2	0	1.1	1	0.2	0	1.1	4	0.3	0.1	0.7	4	0.8	0.2	2.1
Skin and appendages (100)	Dermatitis (0007)	2	0.4	0	1.4	4	0.8	0.2	2.1	5	1	0.3	2.4	11	0.7	0.4	1.3	0	0	0	0.8
	Dermatitis fungal (0009)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Furunculosis (0016)	2	0.4	0	1.4	0	0	0	0.8	1	0.2	0	1.1	3	0.2	0	0.6	0	0	0	0.8
	Photosensitivity reaction (0022)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
	Pruritus (0024)	0	0	0	0.7	3	0.6	0.1	1.8	2	0.4	0	1.5	5	0.3	0.1	0.8	0	0	0	0.8
	Rash (0027)	1	0.2	0	1.1	1	0.2	0	1.1	0	0	0	0.7	2	0.1	0	0.5	0	0	0	0.8
	Rash erythematous (0028)	2	0.4	0	1.4	1	0.2	0	1.1	0	0	0	0.7	3	0.2	0	0.6	1	0.2	0	1.1
	Rash maculo-papular (0030)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	1	0.2	0	1.1
	Rash pustular (0032)	0	0	0	0.7	2	0.4	0	1.5	3	0.6	0.1	1.8	5	0.3	0.1	0.8	2	0.4	0	1.5
	Seborrhea (0033)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Skin disorder (0037)	4	0.8	0.2	2	7	1.4	0.6	2.9	8	1.6	0.7	3.2	19	1.3	0.8	2	7	1.4	0.6	2.9
	Sweat gland disorder (1166)	1	0.2	0	1.1	1	0.2	0	1.1	2	0.4	0	1.5	4	0.3	0.1	0.7	0	0	0	0.8
Urinary system (1300)	Dysuria (0601)	0	0	0	0.7	1	0.2	0	1.1	2	0.4	0	1.5	3	0.2	0	0.6	0	0	0	0.8
	Urinary tract infection (0628)	0	0	0	0.7	0	0	0	0.8	2	0.4	0	1.5	2	0.1	0	0.5	2	0.4	0	1.5
Vision (431)	Blepharitis (1007)	1	0.2	0	1.1	0	0	0	0.8	1	0.2	0	1.1	2	0.1	0	0.5	0	0	0	0.8
	Conjunctivitis (0238)	12	2.4	1.2	4.2	13	2.7	1.4	4.5	9	1.8	0.8	3.4	34	2.3	1.6	3.2	9	1.9	0.9	3.5
White cell and reticuloendothelial system (1220)	Lymphadenopathy cervical (0578)	0	0	0	0.7	0	0	0	0.8	1	0.2	0	1.1	1	0.1	0	0.4	0	0	0	0.8

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 94: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		443	45.3	42.2	48.5	426	44.9	41.7	48.2	416	43.2	40	46.3	1285	44.5	42.7	46.3	419	43.6	40.4	46.8
Application site (1820)	Dermatitis contact (0049)	4	0.4	0.1	1	8	0.8	0.4	1.7	3	0.3	0.1	0.9	15	0.5	0.3	0.9	7	0.7	0.3	1.5
	Injection site reaction (0058)	7	0.7	0.3	1.5	4	0.4	0.1	1.1	5	0.5	0.2	1.2	16	0.6	0.3	0.9	6	0.6	0.2	1.4
	Otitis externa (0059)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.6	1	0	0	0.2	0	0	0	0.4
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.4	2	0.2	0	0.8	1	0.1	0	0.6	3	0.1	0	0.3	1	0.1	0	0.6
	Allergic reaction (0712)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	3	0.3	0.1	0.9
	Allergy (1058)	3	0.3	0.1	0.9	7	0.7	0.3	1.5	5	0.5	0.2	1.2	15	0.5	0.3	0.9	8	0.8	0.4	1.6
	Death, nos (0722)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.6	1	0	0	0.2	0	0	0	0.4
	Fever (0725)	41	4.2	3	5.7	38	4	2.9	5.5	42	4.4	3.2	5.8	121	4.2	3.5	5	34	3.5	2.5	4.9
	Injury (9001)	4	0.4	0.1	1	0	0	0	0.4	0	0	0	0.4	4	0.1	0	0.4	0	0	0	0.4
Cardiovascular general (1010)	Cyanosis (0501)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
Central and peripheral nervous system (410)	Convulsions (0093)	0	0	0	0.4	2	0.2	0	0.8	0	0	0	0.4	2	0.1	0	0.2	1	0.1	0	0.6
	Fever convulsions (1357)	1	0.1	0	0.6	0	0	0	0.4	1	0.1	0	0.6	2	0.1	0	0.2	0	0	0	0.4
	Spasm generalized (0149)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
	Vascular malformation peripheral (0764)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 94 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Gastrointestinal system (600)	Abdominal pain (0268)	32	3.3	2.3	4.6	26	2.7	1.8	4	28	2.9	1.9	4.2	86	3	2.4	3.7	22	2.3	1.4	3.4
	Anorexia (0165)	21	2.1	1.3	3.3	19	2	1.2	3.1	12	1.2	0.6	2.2	52	1.8	1.3	2.4	22	2.3	1.4	3.4
	Anus disorder (0269)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Constipation (0204)	10	1	0.5	1.9	11	1.2	0.6	2.1	10	1	0.5	1.9	31	1.1	0.7	1.5	5	0.5	0.2	1.2
	Gastroenteritis (0293)	2	0.2	0	0.7	5	0.5	0.2	1.2	1	0.1	0	0.6	8	0.3	0.1	0.5	2	0.2	0	0.7
	Gastroesophageal reflux (1149)	4	0.4	0.1	1	6	0.6	0.2	1.4	7	0.7	0.3	1.5	17	0.6	0.3	0.9	3	0.3	0.1	0.9
	Gastrointestinal disorder nos (1262)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.6	1	0	0	0.2	0	0	0	0.4
	Stomatitis (0327)	0	0	0	0.4	1	0.1	0	0.6	1	0.1	0	0.6	2	0.1	0	0.2	1	0.1	0	0.6
	Stomatitis aphthous (0751)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
	Vomiting (0228)	13	1.3	0.7	2.3	17	1.8	1	2.9	12	1.2	0.6	2.2	42	1.5	1	2	18	1.9	1.1	2.9
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Earache (0260)	2	0.2	0	0.7	1	0.1	0	0.6	1	0.1	0	0.6	4	0.1	0	0.4	1	0.1	0	0.6
Neoplasm (1700)	Neoplasm nos (1259)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
Psychiatric (500)	Nervousness (0188)	35	3.6	2.5	4.9	26	2.7	1.8	4	29	3	2	4.3	90	3.1	2.5	3.8	35	3.6	2.5	5
Red blood cell (1210)	Anemia (0544)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 94 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Resistance mechanism (1830)	Abscess (0887)	1	0.1	0	0.6	1	0.1	0	0.6	3	0.3	0.1	0.9	5	0.2	0.1	0.4	0	0	0	0.4
	Infection (0736)	27	2.8	1.8	4	20	2.1	1.3	3.2	17	1.8	1	2.8	64	2.2	1.7	2.8	20	2.1	1.3	3.2
	Infection bacterial (0738)	1	0.1	0	0.6	2	0.2	0	0.8	0	0	0	0.4	3	0.1	0	0.3	1	0.1	0	0.6
	Infection viral (0740)	181	18.5	16.1	21.1	161	17	14.6	19.5	172	17.8	15.5	20.4	514	17.8	16.4	19.2	180	18.7	16.3	21.3
	Moniliasis (0741)	7	0.7	0.3	1.5	10	1.1	0.5	1.9	3	0.3	0.1	0.9	20	0.7	0.4	1.1	4	0.4	0.1	1.1
	Otitis media (0750)	5	0.5	0.2	1.2	11	1.2	0.6	2.1	3	0.3	0.1	0.9	19	0.7	0.4	1	9	0.9	0.4	1.8
	Upper resp tract infection (0543)	45	4.6	3.4	6.1	33	3.5	2.4	4.9	45	4.7	3.4	6.2	123	4.3	3.6	5.1	39	4.1	2.9	5.5
Respiratory system (1100)	Asthma (1367)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Atelectasis (1197)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
	Bronchitis (0805)	19	1.9	1.2	3	21	2.2	1.4	3.4	20	2.1	1.3	3.2	60	2.1	1.6	2.7	12	1.2	0.6	2.2
Respiratory system (1100)	Bronchospasm (0511)	14	1.4	0.8	2.4	8	0.8	0.4	1.7	11	1.1	0.6	2	33	1.1	0.8	1.6	8	0.8	0.4	1.6
	Coughing (0513)	27	2.8	1.8	4	21	2.2	1.4	3.4	27	2.8	1.9	4	75	2.6	2	3.2	18	1.9	1.1	2.9
	Dyspnea (0514)	0	0	0	0.4	1	0.1	0	0.6	1	0.1	0	0.6	2	0.1	0	0.2	1	0.1	0	0.6
	Laryngitis (0521)	1	0.1	0	0.6	3	0.3	0.1	0.9	1	0.1	0	0.6	5	0.2	0.1	0.4	2	0.2	0	0.7
	Pharyngitis (0523)	68	7	5.4	8.7	88	9.3	7.5	11.3	68	7.1	5.5	8.9	224	7.8	6.8	8.8	80	8.3	6.7	10.3
	Pneumonia (0528)	13	1.3	0.7	2.3	23	2.4	1.5	3.6	20	2.1	1.3	3.2	56	1.9	1.5	2.5	20	2.1	1.3	3.2
	Respiratory disorder (0536)	0	0	0	0.4	6	0.6	0.2	1.4	1	0.1	0	0.6	7	0.2	0.1	0.5	2	0.2	0	0.7
	Rhinitis (0539)	7	0.7	0.3	1.5	13	1.4	0.7	2.3	13	1.3	0.7	2.3	33	1.1	0.8	1.6	11	1.1	0.6	2
	Sputum increased (0541)	3	0.3	0.1	0.9	8	0.8	0.4	1.7	1	0.1	0	0.6	12	0.4	0.2	0.7	3	0.3	0.1	0.9
Secondary term (2000)	Varicella (1516)	2	0.2	0	0.7	1	0.1	0	0.6	1	0.1	0	0.6	4	0.1	0	0.4	4	0.4	0.1	1.1

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 94 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Skin and appendages (100)	Dermatitis (0007)	2	0.2	0	0.7	4	0.4	0.1	1.1	5	0.5	0.2	1.2	11	0.4	0.2	0.7	0	0	0	0.4
	Dermatitis fungal (0009)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Furunculosis (0016)	2	0.2	0	0.7	0	0	0	0.4	1	0.1	0	0.6	3	0.1	0	0.3	0	0	0	0.4
	Photosensitivity reaction (0022)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
	Pruritus (0024)	0	0	0	0.4	3	0.3	0.1	0.9	2	0.2	0	0.7	5	0.2	0.1	0.4	0	0	0	0.4
	Rash (0027)	1	0.1	0	0.6	1	0.1	0	0.6	0	0	0	0.4	2	0.1	0	0.2	0	0	0	0.4
	Rash erythematous (0028)	2	0.2	0	0.7	1	0.1	0	0.6	0	0	0	0.4	3	0.1	0	0.3	1	0.1	0	0.6
	Rash maculo-papular (0030)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	1	0.1	0	0.6
	Rash pustular (0032)	0	0	0	0.4	2	0.2	0	0.8	3	0.3	0.1	0.9	5	0.2	0.1	0.4	2	0.2	0	0.7
	Seborrhea (0033)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Skin disorder (0037)	4	0.4	0.1	1	7	0.7	0.3	1.5	9	0.9	0.4	1.8	20	0.7	0.4	1.1	7	0.7	0.3	1.5
	Sweat gland disorder (1166)	1	0.1	0	0.6	1	0.1	0	0.6	2	0.2	0	0.7	4	0.1	0	0.4	0	0	0	0.4
Urinary system (1300)	Dysuria (0601)	0	0	0	0.4	1	0.1	0	0.6	2	0.2	0	0.7	3	0.1	0	0.3	0	0	0	0.4
	Urinary tract infection (0628)	0	0	0	0.4	0	0	0	0.4	2	0.2	0	0.7	2	0.1	0	0.2	3	0.3	0.1	0.9
Vision (431)	Blepharitis (1007)	1	0.1	0	0.6	0	0	0	0.4	1	0.1	0	0.6	2	0.1	0	0.2	0	0	0	0.4
	Conjunctivitis (0238)	12	1.2	0.6	2.1	13	1.4	0.7	2.3	9	0.9	0.4	1.8	34	1.2	0.8	1.6	9	0.9	0.4	1.8
White cell and reticuloendothelial system (1220)	Lymphadenopathy cervical (0578)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.6	1	0	0	0.2	0	0	0	0.4

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 95: Percentage of subjects with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		2	0.4	0	1.4	0	0	0	0.8	0	0	0	0.7	2	0.1	0	0.5	2	0.4	0	1.5
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
	Fever (0725)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
Respiratory system (1100)	Bronchitis (0805)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8

Notes: N = number of subjects having received at least one dose
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 96: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		2	0.2	0	0.7	0	0	0	0.4	0	0	0	0.4	2	0.1	0	0.2	2	0.2	0	0.7
Body as a whole general (1810)	Allergic reaction (0712)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
	Fever (0725)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
Resistance mechanism (1830)	Infection viral (0740)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
Respiratory system (1100)	Bronchitis (0805)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4

Notes:
D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 97: Percentage of subjects with grade "3" unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		13	2.6	1.4	4.4	25	5.1	3.3	7.5	13	2.6	1.4	4.5	51	3.4	2.6	4.5	12	2.5	1.3	4.3
Application site (1820)	Dermatitis contact (0049)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Allergic reaction (0712)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
	Death, nos (0722)	0	0	0	0.7	0	0	0	0.8	1	0.2	0	1.1	1	0.1	0	0.4	0	0	0	0.8
	Fever (0725)	0	0	0	0.7	2	0.4	0	1.5	1	0.2	0	1.1	3	0.2	0	0.6	0	0	0	0.8
Central and peripheral nervous system (410)	Fever convulsions (1357)	1	0.2	0	1.1	0	0	0	0.8	1	0.2	0	1.1	2	0.1	0	0.5	0	0	0	0.8
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.7	0	0	0	0.8	0	0	0	0.7	0	0	0	0.2	1	0.2	0	1.1
Gastrointestinal system (600)	Abdominal pain (0268)	2	0.4	0	1.4	3	0.6	0.1	1.8	1	0.2	0	1.1	6	0.4	0.1	0.9	0	0	0	0.8
	Anorexia (0165)	1	0.2	0	1.1	0	0	0	0.8	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
	Constipation (0204)	0	0	0	0.7	1	0.2	0	1.1	1	0.2	0	1.1	2	0.1	0	0.5	0	0	0	0.8
Gastrointestinal system (600)	Gastroenteritis (0293)	2	0.4	0	1.4	5	1	0.3	2.4	1	0.2	0	1.1	8	0.5	0.2	1.1	2	0.4	0	1.5
	Gastrointestinal disorder nos (1262)	0	0	0	0.7	0	0	0	0.8	1	0.2	0	1.1	1	0.1	0	0.4	0	0	0	0.8

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 97 (continued): Percentage of subjects with grade "3" unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 499				HRV_5.2 N = 487				HRV_5.8 N = 493				Pooled HRV groups N = 1479				Placebo N = 486			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Psychiatric (500)	Nervousness (0188)	1	0.2	0	1.1	0	0	0	0.8	1	0.2	0	1.1	2	0.1	0	0.5	0	0	0	0.8
Resistance	Infection (0736)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	1	0.2	0	1.1
mechanism (1830)	Moniliasis (0741)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
Respiratory system	Asthma (1367)	0	0	0	0.7	1	0.2	0	1.1	0	0	0	0.7	1	0.1	0	0.4	0	0	0	0.8
(1100)	Bronchitis (0805)	2	0.4	0	1.4	3	0.6	0.1	1.8	0	0	0	0.7	5	0.3	0.1	0.8	0	0	0	0.8
	Pharyngitis (0523)	3	0.6	0.1	1.7	6	1.2	0.5	2.7	2	0.4	0	1.5	11	0.7	0.4	1.3	2	0.4	0	1.5
	Pneumonia (0528)	4	0.8	0.2	2	7	1.4	0.6	2.9	5	1	0.3	2.4	16	1.1	0.6	1.8	6	1.2	0.5	2.7

Notes: N = number of subjects having received at least one dose s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 98: Percentage of doses with grade "3" unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		13	1.3	0.7	2.3	25	2.6	1.7	3.9	13	1.3	0.7	2.3	51	1.8	1.3	2.3	13	1.4	0.7	2.3
Application site (1820)	Dermatitis contact (0049)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
Body as a whole general (1810)	Abdomen enlarged (0711)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Allergic reaction (0712)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
	Death, nos (0722)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.6	1	0	0	0.2	0	0	0	0.4
	Fever (0725)	0	0	0	0.4	2	0.2	0	0.8	1	0.1	0	0.6	3	0.1	0	0.3	0	0	0	0.4
Central and peripheral nervous system (410)	Fever convulsions (1357)	1	0.1	0	0.6	0	0	0	0.4	1	0.1	0	0.6	2	0.1	0	0.2	0	0	0	0.4
Fetal (1500)	Urinary tract malformation (0846)	0	0	0	0.4	0	0	0	0.4	0	0	0	0.4	0	0	0	0.1	1	0.1	0	0.6
Gastrointestinal system (600)	Abdominal pain (0268)	2	0.2	0	0.7	3	0.3	0.1	0.9	1	0.1	0	0.6	6	0.2	0.1	0.5	0	0	0	0.4
	Anorexia (0165)	1	0.1	0	0.6	0	0	0	0.4	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Constipation (0204)	0	0	0	0.4	1	0.1	0	0.6	1	0.1	0	0.6	2	0.1	0	0.2	0	0	0	0.4
	Gastroenteritis (0293)	2	0.2	0	0.7	5	0.5	0.2	1.2	1	0.1	0	0.6	8	0.3	0.1	0.5	2	0.2	0	0.7
	Gastrointestinal disorder nos (1262)	0	0	0	0.4	0	0	0	0.4	1	0.1	0	0.6	1	0	0	0.2	0	0	0	0.4

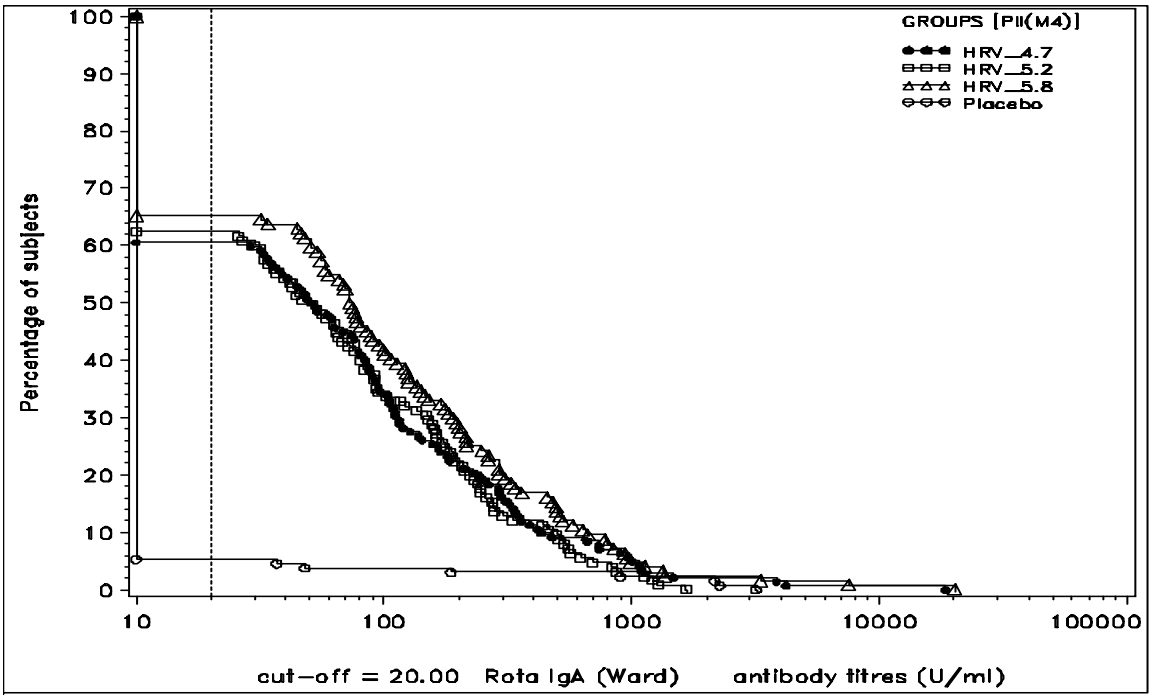
Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 98 (continued): Percentage of doses with grade "3" unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (ATP cohort for safety for subset planned to receive two doses of study vaccine)

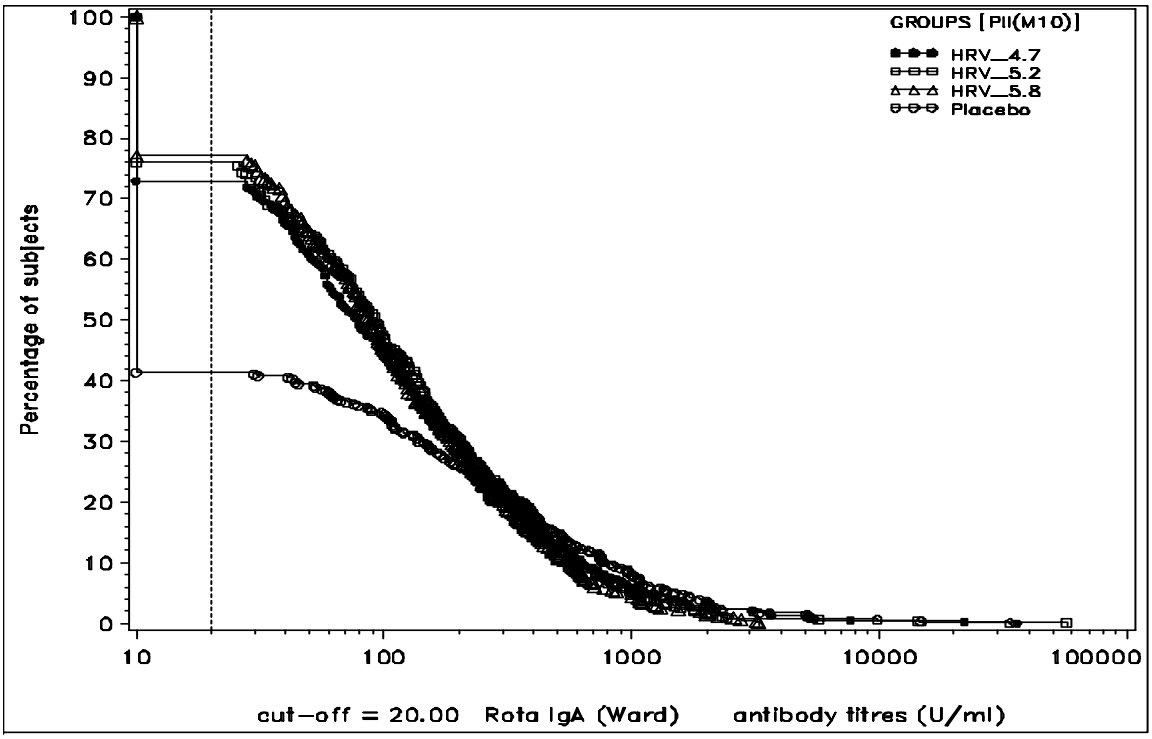
WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 977				HRV_5.2 D = 948				HRV_5.8 D = 964				Pooled HRV groups D = 2889				Placebo D = 961			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Psychiatric (500)	Nervousness (0188)	1	0.1	0	0.6	0	0	0	0.4	1	0.1	0	0.6	2	0.1	0	0.2	0	0	0	0.4
Resistance mechanism (1830)	Infection (0736)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	1	0.1	0	0.6
	Moniliasis (0741)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
Respiratory system (1100)	Asthma (1367)	0	0	0	0.4	1	0.1	0	0.6	0	0	0	0.4	1	0	0	0.2	0	0	0	0.4
	Bronchitis (0805)	2	0.2	0	0.7	3	0.3	0.1	0.9	0	0	0	0.4	5	0.2	0.1	0.4	0	0	0	0.4
	Pharyngitis (0523)	3	0.3	0.1	0.9	6	0.6	0.2	1.4	2	0.2	0	0.7	11	0.4	0.2	0.7	2	0.2	0	0.7
	Pneumonia (0528)	4	0.4	0.1	1	7	0.7	0.3	1.5	5	0.5	0.2	1.2	16	0.6	0.3	0.9	6	0.6	0.2	1.4

Notes: D = Total number of doses administered d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 99: Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations two months after Dose 2 (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 100: Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 101: Results of the exploratory logistic regression to assess impact of feeding criteria on the vaccine take (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Factor	Significance (2 sided P-value)
Exclusive breast feeding	0.464
Breast fed + formula fed	0.848
Fed within 1 hour before vaccination	0.725
Fed within 30 minutes after vaccination	0.273
Group	0.189

Supplement 102: Anti-rotavirus IgA antibody GMC and seroconversion rates in Brazil (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	139	0	0.0	0.0	2.6	<20	-	-
	PI(M2)	57	21	36.8	24.4	50.7	26.2	17.9	38.3
	PII(M4)	53	29	54.7	40.4	68.4	44.8	28.1	71.3
	PII(M10)	131	82	62.6	53.7	70.9	62.5	46.1	84.6
HRV_5.2	PRE	114	0	0.0	0.0	3.2	<20	-	-
	PI(M2)	46	18	39.1	25.1	54.6	28.7	18.4	44.6
	PII(M4)	39	29	74.4	57.9	87.0	84.9	50.3	143.5
	PII(M10)	110	83	75.5	66.3	83.2	93.4	67.7	129.0
HRV_5.8	PRE	120	0	0.0	0.0	3.0	<20	-	-
	PI(M2)	46	18	39.1	25.1	54.6	25.6	17.5	37.6
	PII(M4)	44	28	63.6	47.8	77.6	57.2	35.7	91.6
	PII(M10)	119	80	67.2	58.0	75.6	72.0	53.4	97.1
Pooled HRV groups	PRE	373	0	0.0	0.0	1.0	<20	-	-
	PI(M2)	149	57	38.3	30.4	46.6	26.7	21.3	33.6
	PII(M4)	136	86	63.2	54.5	71.3	58.2	44.1	76.8
	PII(M10)	360	245	68.1	63.0	72.8	74.1	62.0	88.4
Placebo	PRE	116	0	0.0	0.0	3.1	<20	-	-
	PI(M2)	49	3	6.1	1.3	16.9	<20	-	-
	PII(M4)	47	5	10.6	3.5	23.1	<20	-	-
	PII(M10)	112	40	35.7	26.9	45.3	39.5	27.1	57.5

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = two months after the Dose 1
PII(M 4) = two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 103: Anti-rotavirus IgA antibody GMC and seroconversion rates in Mexico (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	76	0	0.0	0.0	4.7	<20	-	-
	PI(M2)	46	22	47.8	32.9	63.1	36.0	22.8	57.0
	PII(M4)	46	31	67.4	52.0	80.5	64.0	40.4	101.4
	PII(M10)	70	59	84.3	73.6	91.9	137.7	94.0	201.8
HRV_5.2	PRE	75	0	0.0	0.0	4.8	<20	-	-
	PI(M2)	38	13	34.2	19.6	51.4	20.0	14.1	28.4
	PII(M4)	40	20	50.0	33.8	66.2	34.1	21.9	53.0
	PII(M10)	70	50	71.4	59.4	81.6	78.0	53.1	114.7
HRV_5.8	PRE	71	0	0.0	0.0	5.1	<20	-	-
	PI(M2	36	23	63.9	46.2	79.2	72.8	39.1	135.3
	PII(M4)	34	24	70.6	52.5	84.9	96.3	53.3	174.0
	PII(M10)	59	49	83.1	71.0	91.6	100.7	69.3	146.4
Pooled HRV groups	PRE	222	0	0.0	0.0	1.6	<20	-	-
	PI(M2)	120	58	48.3	39.1	57.6	36.9	27.7	49.2
	PII(M4)	120	75	62.5	53.2	71.2	58.3	43.8	77.5
	PII(M10)	199	158	79.4	73.1	84.8	102.8	82.5	128.0
Placebo	PRE	64	0	0.0	0.0	5.6	<20	-	-
	PI(M2)	38	0	0.0	0.0	9.3	<20	-	-
	PII(M4)	34	0	0.0	0.0	10.3	<20	-	-
	PII(M10)	61	26	42.6	30.0	55.9	49.5	29.4	83.2

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = two months after the Dose 1
PII(M 4) = two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 104: Anti-rotavirus IgA antibody GMC and seroconversion rates in Venezuela (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	180	0	0.0	0.0	2.0	<20	-	-
	PI(M2)	43	14	32.6	19.1	48.5	20.6	14.7	28.9
	PII(M4)	43	26	60.5	44.4	75.0	56.6	32.8	97.7
	PII(M10)	176	134	76.1	69.1	82.2	75.1	59.8	94.4
HRV_5.2	PRE	185	0	0.0	0.0	2.0	<20	-	-
	PI(M2)	43	17	39.5	25.0	55.6	23.1	16.0	33.5
	PII(M4)	46	29	63.0	47.5	76.8	49.7	31.9	77.4
	PII(M10)	179	140	78.2	71.4	84.0	82.9	66.5	103.5
HRV_5.8	PRE	186	0	0.0	0.0	2.0	<20	-	-
	PI(M2)	50	16	32.0	19.5	46.7	22.1	15.6	31.4
	PII(M4)	46	29	63.0	47.5	76.8	68.9	38.8	122.2
	PII(M10)	176	144	81.8	75.3	87.2	83.2	67.8	102.2
Pooled HRV groups	PRE	551	0	0.0	0.0	0.7	<20	-	-
	PI(M2)	136	47	34.6	26.6	43.2	21.9	18.0	26.8
	PII(M4)	135	84	62.2	53.5	70.4	57.9	43.1	77.8
	PII(M10)	531	418	78.7	75.0	82.1	80.4	70.9	91.1
Placebo	PRE	188	0	0.0	0.0	1.9	<20	-	-
	PI(M2)	52	0	0.0	0.0	6.8	<20	-	-
	PII(M4)	51	2	3.9	0.5	13.5	<20	-	-
	PII(M10)	187	83	44.4	37.1	51.8	43.7	33.4	57.1

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = two months after the Dose 1
PII(M 4) = two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 105: Anti-rotavirus IgA antibody GMC and seroconversion rates (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	534	8	1.5	0.6	2.9	<20.0	-	-
	PI(M2)	187	74	39.6	32.5	47.0	28.2	22.8	35.0
	PII(M4)	180	110	61.1	53.6	68.3	53.6	42.0	68.3
	PII(M10)	472	343	72.7	68.4	76.6	79.9	68.8	92.8
HRV_5.2	PRE	529	8	1.5	0.7	3.0	<20.0	-	-
	PI(M2)	174	74	42.5	35.1	50.2	28.1	22.8	34.7
	PII(M4)	166	107	64.5	56.7	71.7	58.8	45.8	75.4
	PII(M10)	463	361	78.0	73.9	81.7	90.4	78.3	104.3
HRV_5.8	PRE	529	13	2.5	1.3	4.2	<20.0	-	-
	PI(M2)	184	80	43.5	36.2	51.0	31.4	25.3	38.9
	PII(M4)	173	117	67.6	60.1	74.5	67.9	53.1	86.9
	PII(M10)	459	356	77.6	73.5	81.3	88.6	76.7	102.3
Placebo	PRE	528	11	2.1	1.0	3.7	<20.0	-	-
	PI(M2)	192	13	6.8	3.7	11.3	<20.0	-	-
	PII(M4)	182	24	13.2	8.6	19.0	<20.0	-	-
	PII(M10)	488	236	48.4	43.8	52.9	53.0	44.6	62.9

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = blood sample taken at two months after Dose 1
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 106: Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing		GMC		
			Value	95% CI	
		N		LL	UL
HRV_4.7	PRE	8	112.3	39.0	323.4
	PI(M2)	74	137.9	104.8	181.4
	PII(M4)	110	155.9	123.7	196.4
	PII(M10)	343	174.6	153.2	198.9
HRV_5.2	PRE	8	139.8	34.2	572.0
	PI(M2)	74	113.9	87.8	147.7
	PII(M4)	107	156.1	124.3	196.1
	PII(M10)	361	168.3	148.8	190.3
HRV_5.8	PRE	13	134.3	59.5	303.2
	PI(M2)	80	138.5	109.0	176.0
	PII(M4)	117	170.0	137.0	210.8
	PII(M10)	356	166.4	147.1	188.4
Placebo	PRE	11	282.5	101.5	786.8
	PI(M2)	13	299.4	132.5	676.7
	PII(M4)	24	287.2	154.4	534.3
	PII(M10)	236	314.2	268.4	367.9

Notes: N = number of subjects who were seropositive for anti-rotavirus IgA antibodies
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = blood sample taken at two months at two months after Dose 1
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 107: Anti-rotavirus IgA antibody GMC and seroconversion rates in Brazil (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	193	1	0.5	0.0	2.9	<20	-	-
	PI(M2)	73	29	39.7	28.5	51.9	30.8	20.9	45.4
	PII(M4)	67	37	55.2	42.6	67.4	46.1	30.7	69.4
	PII(M10)	177	113	63.8	56.3	70.9	65.8	50.6	85.6
HRV_5.2	PRE	192	0	0.0	0.0	1.9	<20	-	-
	PI(M2)	71	31	43.7	31.9	56.0	31.0	21.9	44.0
	PII(M4)	62	45	72.6	59.8	83.1	73.3	49.9	107.8
	PII(M10)	171	133	77.8	70.8	83.8	98.9	76.8	127.5
HRV_5.8	PRE	191	1	0.5	0.0	2.9	<20	-	-
	PI(M2)	74	31	41.9	30.5	53.9	28.6	20.7	39.5
	PII(M4)	69	44	63.8	51.3	75.0	55.4	38.5	79.7
	PII(M10)	175	122	69.7	62.3	76.4	84.5	65.1	109.8
Pooled HRV groups	PRE	576	2	0.3	0.0	1.2	<20	-	-
	PI(M2)	218	91	41.7	35.1	48.6	30.1	24.6	36.8
	PII(M4)	198	126	63.6	56.5	70.3	56.9	45.6	70.9
	PII(M10)	523	368	70.4	66.2	74.2	81.8	70.4	95.0
Placebo	PRE	192	4	2.1	0.6	5.2	<20	-	-
	PI(M2)	75	9	12.0	5.6	21.6	<20	-	-
	PII(M4)	70	14	20.0	11.4	31.3	<20	-	-
	PII(M10)	179	75	41.9	34.6	49.5	46.2	34.5	61.9

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = two months after the Dose 1
PII(M 4) = two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 108: Anti-rotavirus IgA antibody GMC and seroconversion rates in Mexico (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	99	5	5.1	1.7	11.4	<20	-	-
	PI(M2)	53	27	50.9	36.8	64.9	37.8	24.9	57.5
	PII(M4)	52	36	69.2	54.9	81.3	70.5	45.3	109.7
	PII(M10)	83	71	85.5	76.1	92.3	139.4	99.2	195.9
HRV_5.2	PRE	97	3	3.1	0.6	8.8	<20	-	-
	PI(M2)	50	20	40.0	26.4	54.8	24.9	17.2	36.3
	PII(M4)	52	30	57.7	43.2	71.3	52.8	31.7	88.2
	PII(M10)	86	65	75.6	65.1	84.2	88.0	62.8	123.5
HRV_5.8	PRE	97	4	4.1	1.1	10.2	<20	-	-
	PI(M2)	51	31	60.8	46.1	74.2	57.4	35.1	93.9
	PII(M4)	49	37	75.5	61.1	86.7	98.0	61.9	155.0
	PII(M10)	79	66	83.5	73.5	90.9	96.7	70.9	131.7
Pooled HRV groups	PRE	293	12	4.1	2.1	7.0	<20	-	-
	PI(M2)	154	78	50.6	42.5	58.8	37.9	29.6	48.7
	PII(M4)	153	103	67.3	59.3	74.7	71.0	54.2	93.0
	PII(M10)	248	202	81.5	76.0	86.1	105.8	87.5	127.9
Placebo	PRE	97	5	5.2	1.7	11.6	<20	-	-
	PI(M2)	56	3	5.4	1.1	14.9	<20	-	-
	PII(M4)	52	6	11.5	4.4	23.4	<20	-	-
	PII(M10)	85	46	54.1	43.0	65.0	67.8	44.6	103.1

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = two months after the Dose 1
PII(M 4) = two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 109: Anti-rotavirus IgA antibody GMC and seroconversion rates in Venezuela (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	242	2	0.8	0.1	3.0	<20	-	-
	PI(M2)	61	18	29.5	18.5	42.6	<20	14.7	26.5
	PII(M4)	61	37	60.7	47.3	72.9	50.0	32.6	76.6
	PII(M10)	212	159	75.0	68.6	80.7	75.5	61.4	93.0
HRV_5.2	PRE	240	5	2.1	0.7	4.8	<20	-	-
	PI(M2)	53	23	43.4	29.8	57.7	27.6	18.7	41.0
	PII(M4)	52	32	61.5	47.0	74.7	50.2	32.8	76.9
	PII(M10)	206	163	79.1	72.9	84.5	84.8	69.2	103.9
HRV_5.8	PRE	241	8	3.3	1.4	6.4	<20	-	-
	PI(M2)	59	18	30.5	19.2	43.9	20.9	15.4	28.4
	PII(M4)	55	36	65.5	51.4	77.8	63.3	38.8	103.1
	PII(M10)	205	168	82.0	76.0	87.0	89.1	72.7	109.2
Pooled HRV groups	PRE	723	15	2.1	1.2	3.4	<20	-	-
	PI(M2)	173	59	34.1	27.1	41.7	22.3	18.5	26.9
	PII(M4)	168	105	62.5	54.7	69.8	54.1	41.9	69.7
	PII(M10)	623	490	78.7	75.2	81.8	82.8	73.6	93.2
Placebo	PRE	239	2	0.8	0.1	3.0	<20	-	-
	PI(M2)	61	1	1.6	0.0	8.8	<20	-	-
	PII(M4)	60	4	6.7	1.8	16.2	<20	-	-
	PII(M10)	224	115	51.3	44.6	58.1	53.8	42.1	68.8

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = two months after the Dose 1
PII(M 4) = two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 110: Anti-rotavirus IgA antibody GMC and seroconversion rates for the stool subset (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 20 U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PRE	154	6	3.9	1.4	8.3	<20.0	-	-
	PI(M2)	134	56	41.8	33.3	50.6	30.9	23.8	40.1
	PII(M4)	135	83	61.5	52.7	69.7	56.2	42.2	74.9
	PII(M10)	136	103	75.7	67.6	82.7	100.9	75.6	134.8
HRV_5.2	PRE	150	3	2.0	0.4	5.7	<20.0	-	-
	PI(M2)	127	52	40.9	32.3	50.0	25.9	20.5	32.7
	PII(M4)	126	81	64.3	55.3	72.6	62.7	46.5	84.5
	PII(M10)	127	91	71.7	63.0	79.3	77.6	58.1	103.5
HRV_5.8	PRE	148	2	1.4	0.2	4.8	<20.0	-	-
	PI(M2)	136	58	42.6	34.2	51.4	31.0	24.0	40.1
	PII(M4)	131	87	66.4	57.6	74.4	64.9	48.8	86.3
	PII(M10)	126	94	74.6	66.1	81.9	88.1	66.4	116.8
Placebo	PRE	149	3	2.0	0.4	5.8	<20.0	-	-
	PI(M2)	144	5	3.5	1.1	7.9	<20.0	-	-
	PII(M4)	138	16	11.6	6.8	18.1	<20.0	-	-
	PII(M10)	134	65	48.5	39.8	57.3	54.9	39.4	76.4

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the cut-off
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PRE = pre-vaccination
PI(M 2) = blood sample taken at two months after Dose 1
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = at the end of the first efficacy period

Supplement 111: Percentage of subjects with rotavirus in stool samples collected at pre-determined time points (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Shedding Dose 1								
	Day 0 [Day –1 to Day 0]			[Day 1 to Day 5]			Day 7 [Day 6 to Day 10]		
	N	n	%	N	n	%	N	n	%
HRV-10$^{4.7}$	144	0	0.0	1	0	0.0	136	45	33.1
HRV-10$^{5.2}$	139	0	0.0	1	0	0.0	135	47	34.8
HRV-10$^{5.8}$	136	1	0.7	5	1	20.0	136	59	43.4
Placebo	137	0	0.0	3	0	0.0	135	1	0.7

Group	Shedding Dose 1					
	[Day 11 to Day 12]			Day 60 [Day –6 to Day o of Dose 2]		
	N	n	%	N	n	%
HRV-10$^{4.7}$	1	1	100.0	130	0	0.0
HRV-10$^{5.2}$	2	1	50.0	118	1	0.8
HRV-10$^{5.8}$	2	0	0.0	124	1	0.8
Placebo	0	-	-	132	2	1.5

Group	Shedding Dose 2								
	[Day 1 to Day 5]			Day 7 [Day 6 to Day 10]			[Day 11 to Day 16]		
	N	n	%	N	n	%	N	n	%
HRV-10$^{4.7}$	6	0	0.0	117	15	12.8	5	0	0.0
HRV-10$^{5.2}$	4	1	25.0	118	24	20.3	3	0	0.0
HRV-10$^{5.8}$	7	1	14.3	123	22	17.9	6	0	0.0
Placebo	3	0	0.0	127	1	0.8	4	0	0.0

Notes: N = number of subject with available stool results at the specified time point
n/% = number/percentage of subjects with rotavirus in stool collected at the specified time point

Supplement 112: Percentage of subjects with rotavirus in stool samples collected at pre-determined time points, on combined time points (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Shedding – Combined timepoints				
	N	n	%	95%CI L.L.	U.L.
HRV-10$^{4.7}$	154	57	37.0	29.4	45.2
HRV-10$^{5.2}$	154	68	44.2	36.2	52.4
HRV-10$^{5.8}$	154	75	48.7	40.6	56.9
Placebo	155	4	2.6	0.7	6.5

Notes: N = number of subject with available stool results for at least one time point
n/% = number/percentage of subjects with rotavirus in at least one stool
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 113: Difference between pooled/each HRV vaccine groups and the placebo group in anti-diphtheria antibody seroprotection rates, at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Diphtheria seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	133	70.7	HRV _4.7	146	64.4	Placebo minus HRV _4.7	6.3	-4.7	17.1
			HRV _5.2	136	58.8	Placebo minus HRV _5.2	11.9	0.4	23.0
			HRV _5.8	130	75.4	Placebo minus HRV _5.8	-4.7	-15.4	6.1
			Pooled HRV Groups	412	66.0	Placebo minus Pooled HRV Groups	4.7	-4.7	13.2

Notes: N = number of subjects with available results
% = percentage of subjects with anti-diphtheria antibody concentrations ≥ 0.1 IU/ml (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 114: Difference between pooled/each HRV vaccine groups and the placebo group in anti-diphtheria antibody seroprotection rates, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Diphtheria seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	149	74.5	HRV _4.7	164	70.1	Placebo minus HRV _4.7	4.4	-5.6	14.2
			HRV _5.2	149	68.5	Placebo minus HRV _5.2	6.0	-4.2	16.2
			HRV _5.8	142	70.4	Placebo minus HRV _5.8	4.1	-6.2	14.3
			Pooled HRV Groups	455	69.7	Placebo minus Pooled HRV Groups	4.8	-3.7	12.6

Notes: N = number of subjects with available results
% = percentage of subjects with anti-diphtheria antibody concentrations ≥ 0.1 IU/ml (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 115: Ratio of anti-diphtheria antibody GMCs between pooled/each HRV vaccine groups and the placebo group, at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	133	0.3	HRV _4.7	146	0.2	Placebo over HRV _4.7	1.36	0.99	1.86
			HRV _5.2	136	0.2	Placebo over HRV _5.2	1.51	1.10	2.08
			HRV _5.8	130	0.2	Placebo over HRV _5.8	1.12	0.81	1.55
						Placebo over Pooled HRV Groups*	1.32	1.02	1.72

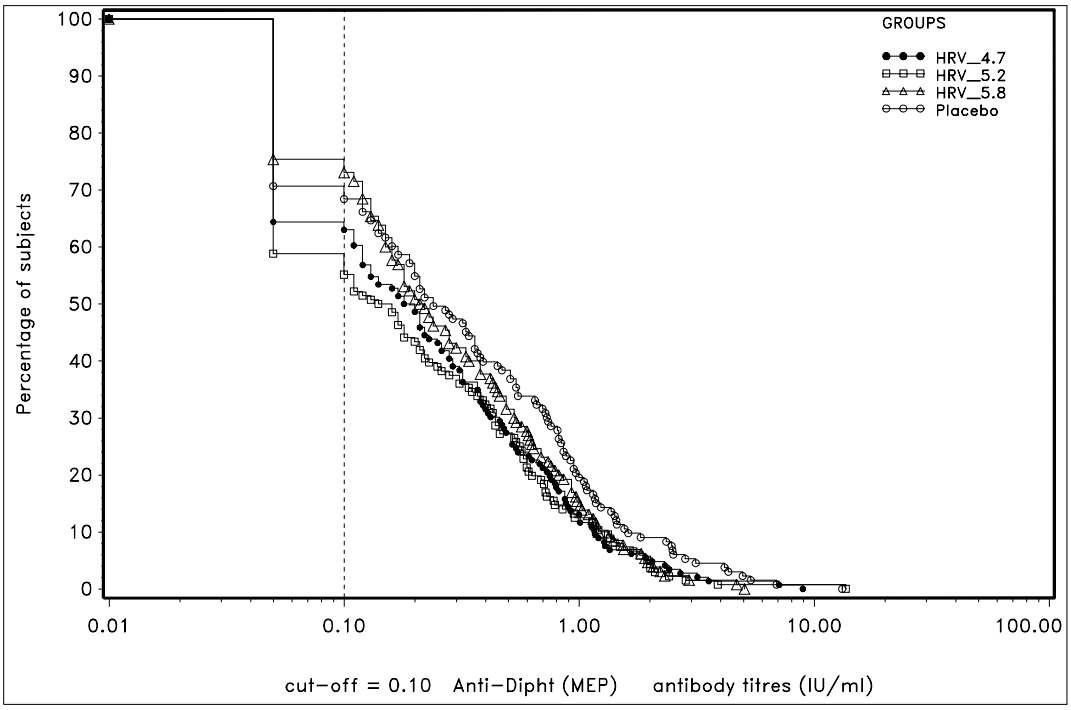
Notes: N = number of subjects with available data
95%CI, LL, UL = 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 116: Ratio of anti-diphtheria antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

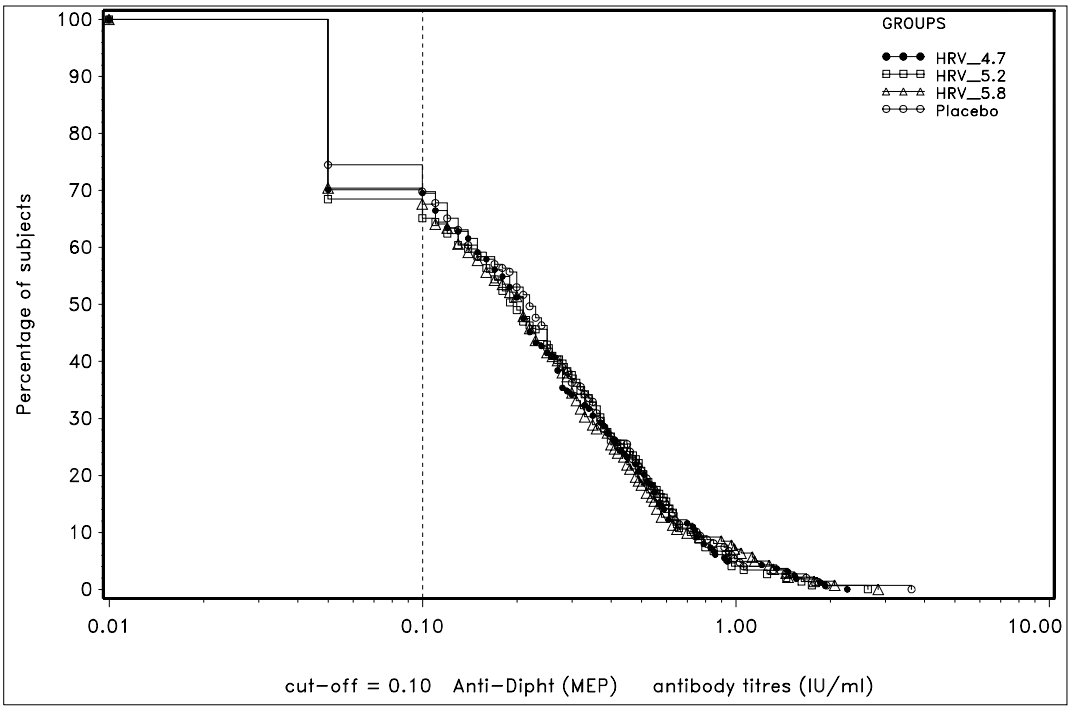
						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	149	0.2	HRV _4.7	164	0.2	Placebo over HRV _4.7	1.06	0.84	1.35
			HRV _5.2	149	0.2	Placebo over HRV _5.2	1.08	0.85	1.38
			HRV _5.8	142	0.2	Placebo over HRV _5.8	1.07	0.84	1.37
						Placebo over Pooled HRV Groups*	1.07	0.88	1.31

Notes: N = number of subjects with available data
95%CI, LL, UL = 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 117: Reverse cumulative curve for anti-diphtheria antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 118: Reverse cumulative curve for anti-diphtheria antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 119: Difference between pooled/each HRV vaccine groups and the placebo group in anti-tetanus antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Tetanus seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	134	99.3	HRV _4.7	147	98.6	Placebo minus HRV _4.7	0.6	-2.9	4.2
			HRV _5.2	136	100.0	Placebo minus HRV _5.2	-0.7	-4.1	2.0
			HRV _5.8	131	97.7	Placebo minus HRV _5.8	1.5	-2.0	5.9
			Pooled HRV Groups	414	98.8	Placebo minus Pooled HRV Groups	0.5	-2.9	2.2

Notes: N = number of subjects with available results
% = percentage of subjects with anti-tetanus antibody concentrations ≥ 0.1 IU/ml (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 120: Difference between pooled/each HRV vaccine groups and the placebo group in anti-tetanus antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Tetanus seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	149	100.0	HRV _4.7	166	100.0	Placebo minus HRV _4.7	0.0	-2.5	2.3
			HRV _5.2	150	98.7	Placebo minus HRV _5.2	1.3	-1.2	4.7
			HRV _5.8	143	100.0	Placebo minus HRV _5.8	0.0	-2.5	2.6
			Pooled HRV Groups	459	99.6	Placebo minus Pooled HRV Groups	0.4	-2.1	1.6

Notes: N = number of subjects with available results
% = percentage of subjects with anti-tetanus antibody concentrations ≥ 0.1 IU/ml (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 121: Ratio of anti-tetanus antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	N	GMC	Group	N	GMC	GMC ratio Groups	Value %	95% CI LL	UL
Placebo	134	1.2	HRV _4.7	147	1.1	Placebo over HRV _4.7	1.05	0.81	1.35
			HRV _5.2	136	1.1	Placebo over HRV _5.2	1.06	0.82	1.37
			HRV _5.8	131	1.1	Placebo over HRV _5.8	1.10	0.85	1.43
						Placebo over Pooled HRV Groups*	1.07	0.87	1.32

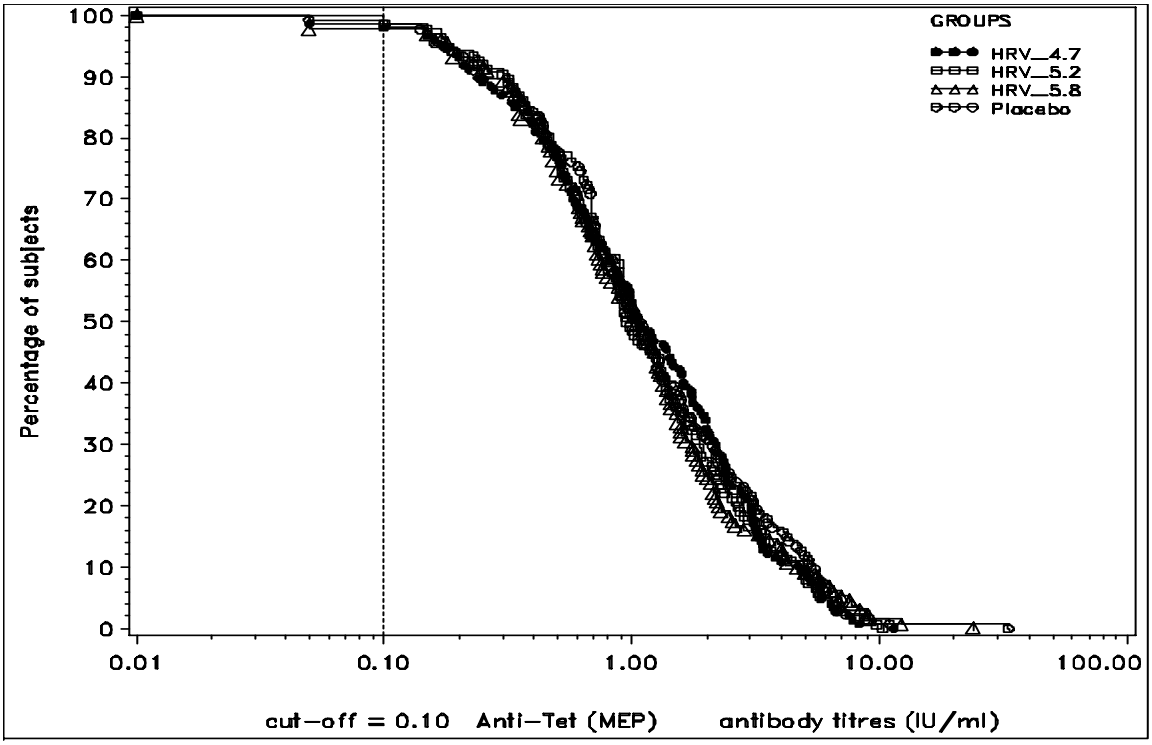
Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 122: Ratio of anti-tetanus antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

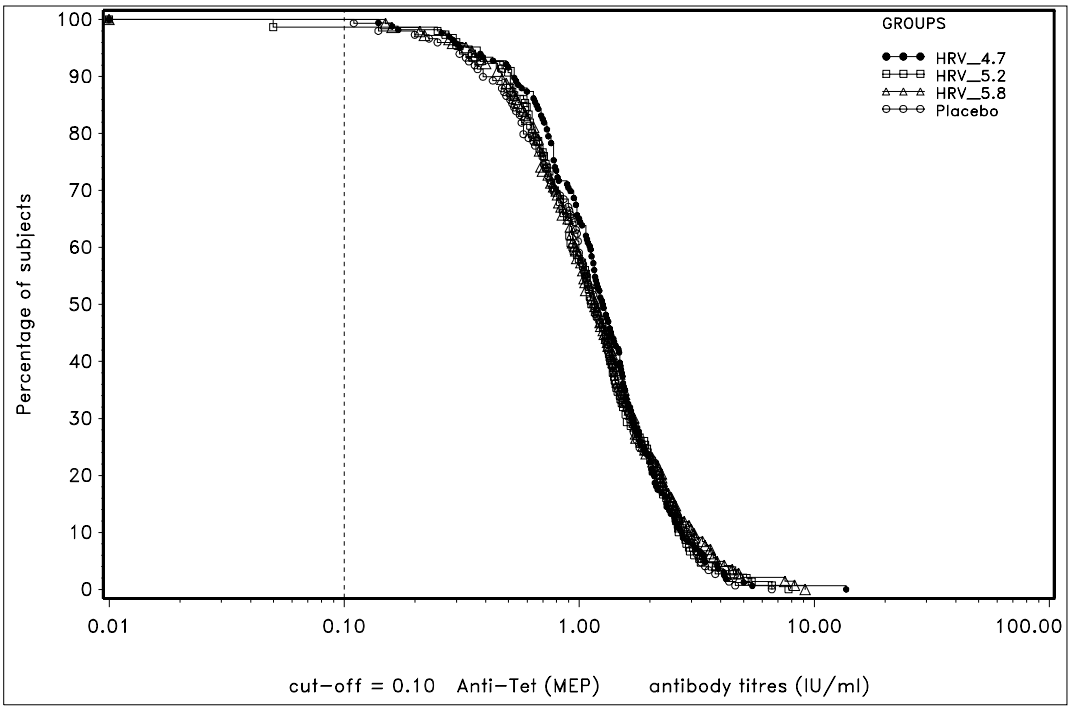
Group	N	GMC	Group	N	GMC	GMC ratio Groups	Value %	95% CI LL	UL
Placebo	149	1.1	HRV _4.7	166	1.2	Placebo over HRV _4.7	0.91	0.77	1.07
			HRV _5.2	150	1.1	Placebo over HRV _5.2	0.98	0.83	1.16
			HRV _5.8	143	1.2	Placebo over HRV _5.8	0.95	0.80	1.13
						Placebo over Pooled HRV Groups*	0.95	0.83	1.09

Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 123: Reverse cumulative curve for anti-tetanus antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 124: Reverse cumulative curve for anti-tetanus antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 125: Difference between pooled/each HRV vaccine groups and the placebo group in anti-BPT antibody seropositivity rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-BPT seropositivity			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	130	61.5	HRV _4.7	144	65.3	Placebo minus HRV _4.7	-3.7	-15.1	7.6
			HRV _5.2	134	59.0	Placebo minus HRV _5.2	2.6	-9.2	14.3
			HRV _5.8	131	64.1	Placebo minus HRV _5.8	-2.6	-14.2	9.1
			Pooled HRV Groups	409	62.8	Placebo minus Pooled HRV Groups	-1.3	-11.0	8.0

Notes: N = number of subjects with available results
% = percentage of subjects with anti-BPT antibody concentrations ≥ 15 EL.U/ml (seropositivity)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 126: Difference between pooled/each HRV vaccine groups and the placebo group in anti-BPT seropositivity rates at the end of the first efficacy period (ATP cohort for immunogenicity)

						Difference in anti-BPT seropositivity			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	148	71.6	HRV _4.7	165	75.2	Placebo minus HRV _4.7	-3.5	-13.4	6.2
			HRV _5.2	151	80.1	Placebo minus HRV _5.2	-8.5	-18.2	1.2
			HRV _5.8	144	70.1	Placebo minus HRV _5.8	1.5	-8.9	11.9
			Pooled HRV Groups	460	75.2	Placebo minus Pooled HRV Groups	-3.6	-12.2	4.3

Notes: N = number of subjects with available results
% = percentage of subjects with anti-BPT antibody concentrations ≥ 15 EL.U/ml (seropositivity)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 127: Ratio of anti-BPT antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	N	GMC	Group	N	GMC	GMC ratio Groups	Value %	95% CI LL	UL
Placebo	130	17.6	HRV _4.7	144	19.4	Placebo over HRV _4.7	0.91	0.75	1.10
			HRV _5.2	134	18.5	Placebo over HRV _5.2	0.95	0.78	1.15
			HRV _5.8	131	18.4	Placebo over HRV _5.8	0.96	0.79	1.16
						Placebo over Pooled HRV Groups*	0.94	0.80	1.10

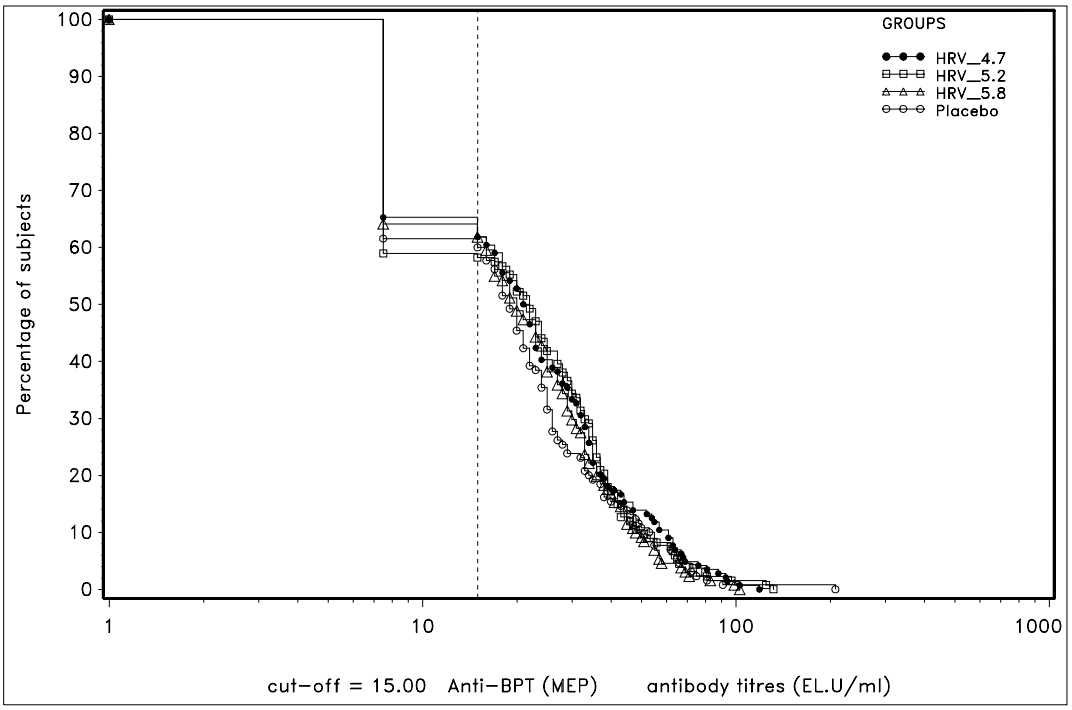
Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 128: Ratio of anti-BPT antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

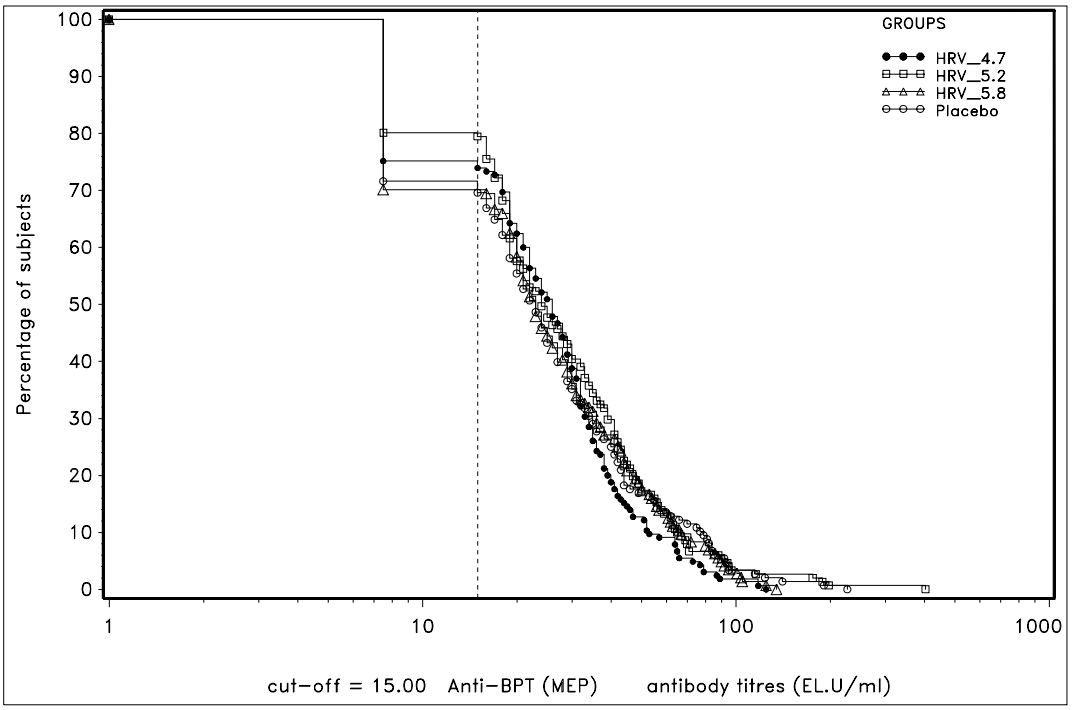
Group	N	GMC	Group	N	GMC	GMC ratio Groups	Value %	95% CI LL	UL
Placebo	148	22.4	HRV _4.7	165	22.5	Placebo over HRV _4.7	0.99	0.83	1.19
			HRV _5.2	151	25.2	Placebo over HRV _5.2	0.89	0.74	1.07
			HRV _5.8	144	22.2	Placebo over HRV _5.8	1.01	0.83	1.21
						Placebo over Pooled HRV Groups*	0.96	0.83	1.12

Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 129: Reverse cumulative curve for anti-BPT antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 130: Reverse cumulative curve for anti-BPT antibody concentrations at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 131: Difference between pooled/each HRV vaccine groups and the placebo group in anti-HBs antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-HBS seroportection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	133	98.5	HRV _4.7	147	98.6	Placebo minus HRV _4.7	-0.1	-4.1	3.5
			HRV _5.2	136	98.5	Placebo minus HRV _5.2	0.0	-4.0	3.9
			HRV _5.8	134	97.0	Placebo minus HRV _5.8	1.5	-2.7	6.1
			Pooled HRV Groups	417	98.1	Placebo minus Pooled HRV Groups	0.4	-3.5	2.6

Notes: N = number of subjects with available results
% = percentage of subjects with anti-HBs antibody concentrations ≥ 10 mIU/ml (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 132: Difference between pooled/each HRV vaccine groups and the placebo group in anti-HBs antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-HBS seroportection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	149	96.6	HRV _4.7	165	95.2	Placebo minus HRV _4.7	1.5	-3.4	6.4
			HRV _5.2	150	96.7	Placebo minus HRV _5.2	0.0	-4.7	4.6
			HRV _5.8	143	97.9	Placebo minus HRV _5.8	-1.3	-5.8	3.0
			Pooled HRV Groups	458	96.5	Placebo minus Pooled HRV Groups	0.1	-4.3	3.0

Notes: N = number of subjects with available results
% = percentage of subjects with anti-HBs antibody concentrations ≥ 10 mIU/ml (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 133: Ratio of anti-HBs antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	N	GMC	Group	N	GMC	GMC ratio Groups	Value %	95% CI LL	UL
Placebo	133	674.9	HRV _4.7	147	550.6	Placebo over HRV _4.7	1.23	0.89	1.69
			HRV _5.2	136	595.7	Placebo over HRV _5.2	1.13	0.82	1.57
			HRV _5.8	134	515.9	Placebo over HRV _5.8	1.31	0.94	1.82
						Placebo over Pooled HRV Groups*	1.22	0.93	1.60

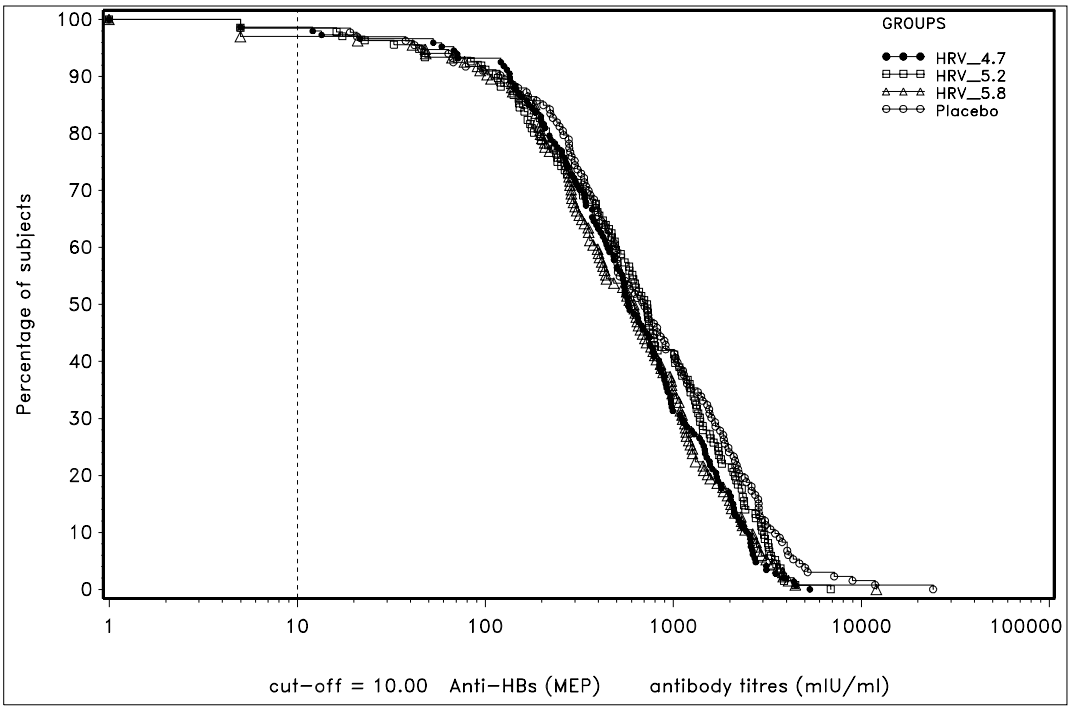
Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 134: Ratio of anti-HBs antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

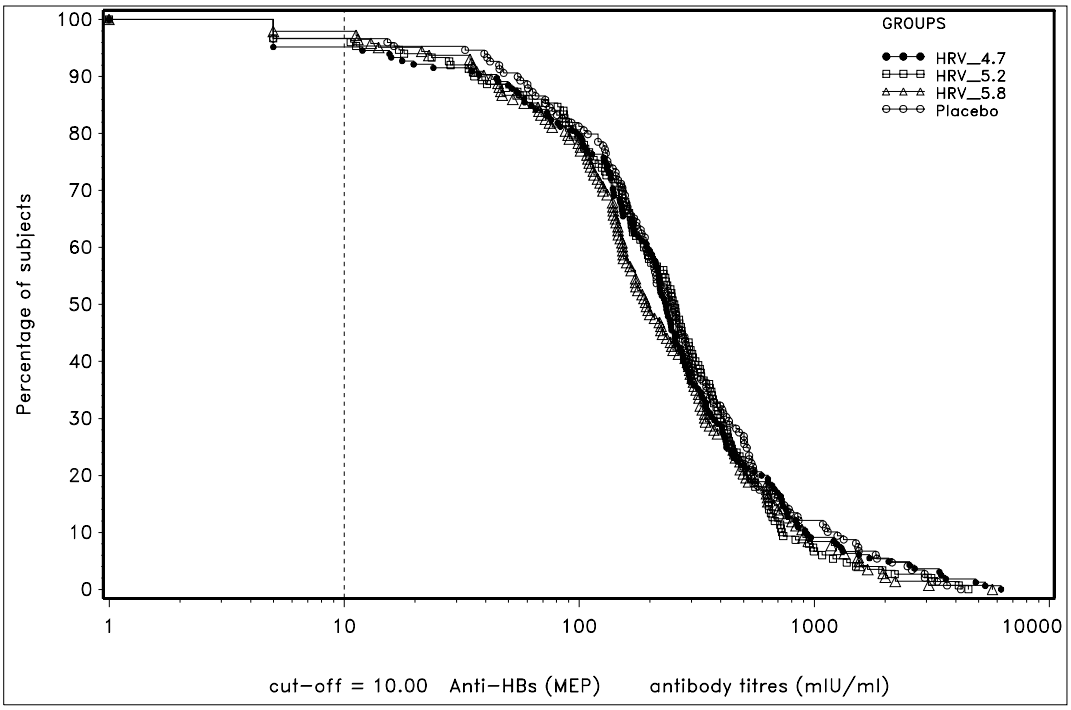
Group	N	GMC	Group	N	GMC	GMC ratio Groups	Value %	95% CI LL	UL
Placebo	149	238.7	HRV _4.7	165	212.7	Placebo over HRV _4.7	1.12	0.84	1.50
			HRV _5.2	150	214.4	Placebo over HRV _5.2	1.11	0.83	1.50
			HRV _5.8	143	200.0	Placebo over HRV _5.8	1.19	0.88	1.62
						Placebo over Pooled HRV Groups*	1.14	0.89	1.46

Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 135: Reverse cumulative curve for anti-HBs antibody concentrations at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 136: Reverse cumulative curve for anti-HBs antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 137: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP concentrations ≥ 0.15 mcg/ml at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity)

						Difference in percentage of subjects with anti-PRP concentrations ≥ 0.15 mcg/ml			
Group	**N**	**%**	**Group**	**N**	**%**	**Groups**	**Value %**	**95% CI LL**	**UL**
Placebo	131	99.2	HRV _4.7	143	100.0	Placebo minus HRV _4.7	-0.8	-4.2	1.9
			HRV _5.2	136	99.3	Placebo minus HRV _5.2	0.0	-3.5	3.4
			HRV _5.8	133	99.2	Placebo minus HRV _5.8	0.0	-3.5	3.4
			Pooled HRV Groups	412	99.5	Placebo minus Pooled HRV Groups	-0.3	-3.7	1.1

Notes: N = number of subjects with available results
% = percentage of subjects with anti-PRP antibody concentrations ≥ 0.15 mcg/ml
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 138: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP antibody concentrations ≥ 1 mcg/ml at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in percentage of subjects with anti-PRP concentrations ≥ 1 mcg/ml			
Group	**N**	**%**	**Group**	**N**	**%**	**Groups**	**Value %**	**95% CI LL**	**UL**
Placebo	131	89.3	HRV _4.7	143	96.5	Placebo minus HRV _4.7	-7.2	-14.1	-1.3
			HRV _5.2	136	88.2	Placebo minus HRV _5.2	1.1	-6.8	8.9
			HRV _5.8	133	91.0	Placebo minus HRV _5.8	-1.7	-9.2	5.8
			Pooled HRV Groups	412	92.0	Placebo minus Pooled HRV Groups	-2.7	-9.5	2.5

Notes: N = number of subjects with available results
% = percentage of subjects with anti-PRP antibody concentrations ≥ 1 mcg/ml
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 139: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP antibody concentrations ≥ 0.15 mcg/ml at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in percentage of subjects with anti-PRP concentrations ≥ 0.15 mcg/ml			
							Value	**95% CI**	
Group	**N**	**%**	**Group**	**N**	**%**	**Groups**	**%**	**LL**	**UL**
Placebo	149	100.0	HRV _4.7	165	99.4	Placebo minus HRV _4.7	0.6	-1.9	3.4
			HRV _5.2	149	99.3	Placebo minus HRV _5.2	0.7	-1.9	3.7
			HRV _5.8	143	100.0	Placebo minus HRV _5.8	0.0	-2.5	2.6
			Pooled HRV Groups	457	99.6	Placebo minus Pooled HRV Groups	0.4	-2.1	1.6

Notes: N = number of subjects with available results
% = percentage of subjects with anti-PRP antibody concentrations ≥ 0.15 mcg/ml
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 140: Difference between pooled/each HRV vaccine groups and the placebo group in percentage of subjects with anti-PRP antibody concentrations ≥ 1 mcg/ml ml at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in percentage of subjects with anti-PRP concentrations ≥ 1 mcg/ml			
							Value	**95% CI**	
Group	**N**	**%**	**Group**	**N**	**%**	**Groups**	**%**	**LL**	**UL**
Placebo	149	94.6	HRV _4.7	165	93.9	Placebo minus HRV _4.7	0.7	-4.9	6.2
			HRV _5.2	149	91.3	Placebo minus HRV _5.2	3.4	-2.6	9.7
			HRV _5.8	143	91.6	Placebo minus HRV _5.8	3.0	-3.0	9.4
			Pooled HRV Groups	457	92.3	Placebo minus Pooled HRV Groups	2.3	-3.0	6.2

Notes: N = number of subjects with available results
% = percentage of subjects with anti-PRP antibody concentrations ≥ 1 mcg/ml
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 141: Ratio of anti-PRP antibody GMCs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	131	5.1	HRV _4.7	143	6.4	Placebo over HRV _4.7	0.79	0.59	1.06
			HRV _5.2	136	5.6	Placebo over HRV _5.2	0.90	0.67	1.21
			HRV _5.8	133	5.1	Placebo over HRV _5.8	0.99	0.74	1.34
						Placebo over Pooled HRV Groups*	0.89	0.70	1.13

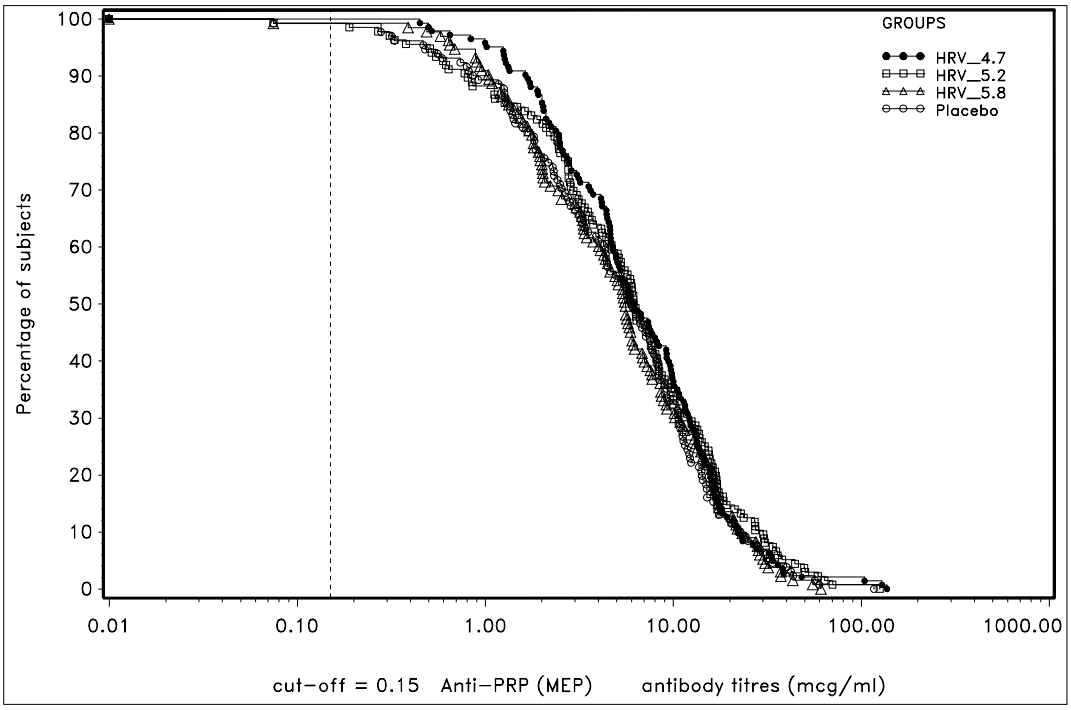
Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
*For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 142: Ratio of anti-PRP antibody GMCs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

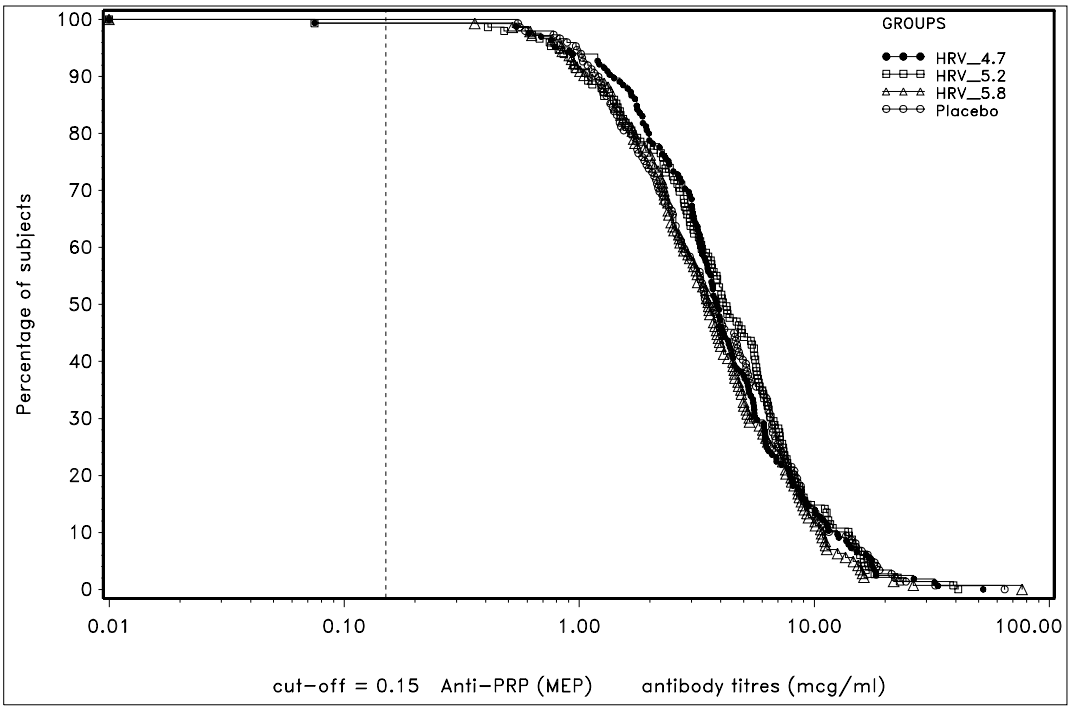
						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	149	3.8	HRV _4.7	165	4.0	Placebo over HRV _4.7	0.96	0.79	1.18
			HRV _5.2	149	4.0	Placebo over HRV _5.2	0.96	0.78	1.18
			HRV _5.8	143	3.6	Placebo over HRV _5.8	1.07	0.87	1.32
						Placebo over Pooled HRV Groups*	0.99	0.84	1.18

Notes: N = Number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMC ratio is derived as the geometric mean of the 3 individual GMC ratios

Supplement 143: Reverse cumulative curve for anti-PRP antibody concentrations, at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 144: Reverse cumulative curve for anti-PRP antibody concentrations, at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 145: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 1 antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Polio 1 seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	130	99.2	HRV _4.7	147	98.6	Placebo minus HRV _4.7	0.6	-3.0	4.1
			HRV _5.2	135	97.8	Placebo minus HRV _5.2	1.5	-2.2	5.7
			HRV _5.8	133	98.5	Placebo minus HRV _5.8	0.7	-2.9	4.6
			Pooled HRV Groups	415	98.3	Placebo minus Pooled HRV Groups	0.9	-2.6	2.8

Notes: N = number of subjects with available results
% = percentage of subjects with anti-poliovirus type 1 antibody titers ≥ 8 ED50 (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 146: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 2 antibody seroprotection at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Polio 2 seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	130	99.2	HRV _4.7	147	98.6	Placebo minus HRV _4.7	0.6	-3.0	4.1
			HRV _5.2	135	99.3	Placebo minus HRV _5.2	0.0	-3.6	3.4
			HRV _5.8	133	99.2	Placebo minus HRV _5.8	0.0	-3.5	3.4
			Pooled HRV Groups	415	99.0	Placebo minus Pooled HRV Groups	0.2	-3.3	1.9

Notes: N = number of subjects with available results
% = percentage of subjects with anti-poliovirus type 2 antibody titers ≥ 8 ED50 (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 147: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 3 antibody seroprotection rates at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Polio 3 seroprotection rates			
							Value	95% CI	
Group	N	%	Group	N	%	Groups	%	LL	UL
Placebo	130	84.6	HRV _4.7	147	87.1	Placebo minus HRV _4.7	-2.5	-11.0	5.8
			HRV _5.2	135	84.4	Placebo minus HRV _5.2	0.2	-8.7	9.0
			HRV _5.8	133	89.5	Placebo minus HRV _5.8	-4.9	-13.3	3.3
			Pooled HRV Groups	415	87.0	Placebo minus Pooled HRV Groups	-2.4	-10.1	4.0

Notes: N = number of subjects with available results
% = percentage of subjects with anti-poliovirus type 3 antibody titers ≥ 8 ED50 (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 148: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 1 antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Polio 1 seroprotection rates			
							Value	**95% CI**	
Group	**N**	**%**	**Group**	**N**	**%**	**Groups**	**%**	**LL**	**UL**
Placebo	138	100.0	HRV _4.7	156	99.4	Placebo minus HRV _4.7	0.6	-2.1	3.5
			HRV _5.2	139	100.0	Placebo minus HRV _5.2	0.0	-2.7	2.7
			HRV _5.8	134	100.0	Placebo minus HRV _5.8	0.0	-2.7	2.8
			Pooled HRV Groups	429	99.8	Placebo minus Pooled HRV Groups	0.2	-2.5	1.3

Notes:
N = number of subjects with available results
% = percentage of subjects with anti-poliovirus type 1 antibody titers ≥ 8 ED50 (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 149: Difference between pooled/each HRV vaccine groups and the placebo group in anti-poliovirus type 2 antibody seroprotection at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Polio 2 seroprotection rates			
							Value	95% CI	
Group	**N**	**%**	**Group**	**N**	**%**	**Groups**	**%**	**LL**	**UL**
Placebo	148	99.3	HRV _4.7	164	98.8	Placebo minus HRV _4.7	0.5	-2.6	3.7
			HRV _5.2	147	100.0	Placebo minus HRV _5.2	-0.7	-3.7	1.9
			HRV _5.8	140	100.0	Placebo minus HRV _5.8	-0.7	-3.7	2.0
			Pooled HRV Groups	451	99.6	Placebo minus Pooled HRV Groups	-0.2	-3.3	1.1

Notes: N = number of subjects with available results
% = percentage of subjects with anti-poliovirus type 2 antibody titers ≥ 8 ED50 (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 150: Difference between pooled/ each HRV vaccine groups and the placebo group in anti-poliovirus type 3 antibody seroprotection rates at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						Difference in anti-Polio 3 seroprotection rates			
							Value	**95% CI**	
Group	**N**	**%**	**Group**	**N**	**%**	**Groups**	**%**	**LL**	**UL**
Placebo	148	93.2	HRV _4.7	164	92.1	Placebo minus HRV _4.7	1.2	-5.0	7.2
			HRV _5.2	147	91.2	Placebo minus HRV _5.2	2.1	-4.3	8.6
			HRV _5.8	140	95.0	Placebo minus HRV _5.8	-1.8	-7.7	4.0
			Pooled HRV Groups	451	92.7	Placebo minus Pooled HRV Groups	0.6	-5.0	4.7

Notes: N = number of subjects with available results
% = percentage of subjects with anti-poliovirus type 3 antibody titers ≥ 8 ED50 (seroprotection)
CI = standardized asymptotic confidence interval; LL = Lower Limit; UL = Upper Limit

Supplement 151: Ratio of anti-poliovirus type 1 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	130	1322.7	HRV _4.7	147	1546.9	Placebo over HRV _4.7	0.86	0.60	1.22
			HRV _5.2	135	1120.1	Placebo over HRV _5.2	1.18	0.82	1.70
			HRV _5.8	133	1261.4	Placebo over HRV _5.8	1.05	0.73	1.51
						Placebo over Pooled HRV Groups*	1.01	0.75	1.36

Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMT ratio is derived as the geometric mean of the 3 individual GMT ratios

Supplement 152: Ratio of anti-poliovirus type 2 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	130	1112.1	HRV _4.7	147	1138.6	Placebo over HRV _4.7	0.98	0.72	1.32
			HRV _5.2	135	1042.7	Placebo over HRV _5.2	1.10	0.78	1.45
			HRV _5.8	133	1346.2	Placebo over HRV _5.8	0.83	0.61	1.12
						Placebo over Pooled HRV Groups*	0.95	0.74	1.23

Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
For the pooled HRV group, the GMT ratio is derived as the geometric mean of the 3 individual GMT ratios

Supplement 153: Ratio of anti-poliovirus type 3 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	130	155.5	HRV _4.7	147	184.1	Placebo over HRV _4.7	0.84	0.55	1.31
			HRV _5.2	135	158.0	Placebo over HRV _5.2	0.98	0.63	1.53
			HRV _5.8	133	181.1	Placebo over HRV _5.8	0.86	0.55	1.34
						Placebo over Pooled HRV Groups*	0.89	0.62	1.28

Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMT ratio is derived as the geometric mean of the 3 individual GMT ratios

Supplement 154: Ratio of anti-poliovirus type 1 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	138	693.9	HRV _4.7	156	802.1	Placebo over HRV _4.7	0.87	0.66	1.14
			HRV _5.2	139	731.3	Placebo over HRV _5.2	0.95	0.71	1.26
			HRV _5.8	134	714.8	Placebo over HRV _5.8	0.97	0.73	1.29
						Placebo over Pooled HRV Groups*	0.92	0.73	1.17

Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMT ratio is derived as the geometric mean of the 3 individual GMT ratios

Supplement 155: Ratio of anti-poliovirus type 2 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	148	438.7	HRV _4.7	164	469.7	Placebo over HRV _4.7	0.93	0.74	1.18
			HRV _5.2	147	472.6	Placebo over HRV _5.2	0.93	0.73	1.18
			HRV _5.8	140	523.6	Placebo over HRV _5.8	0.84	0.66	1.07
						Placebo over Pooled HRV Groups*	0.90	0.74	1.09

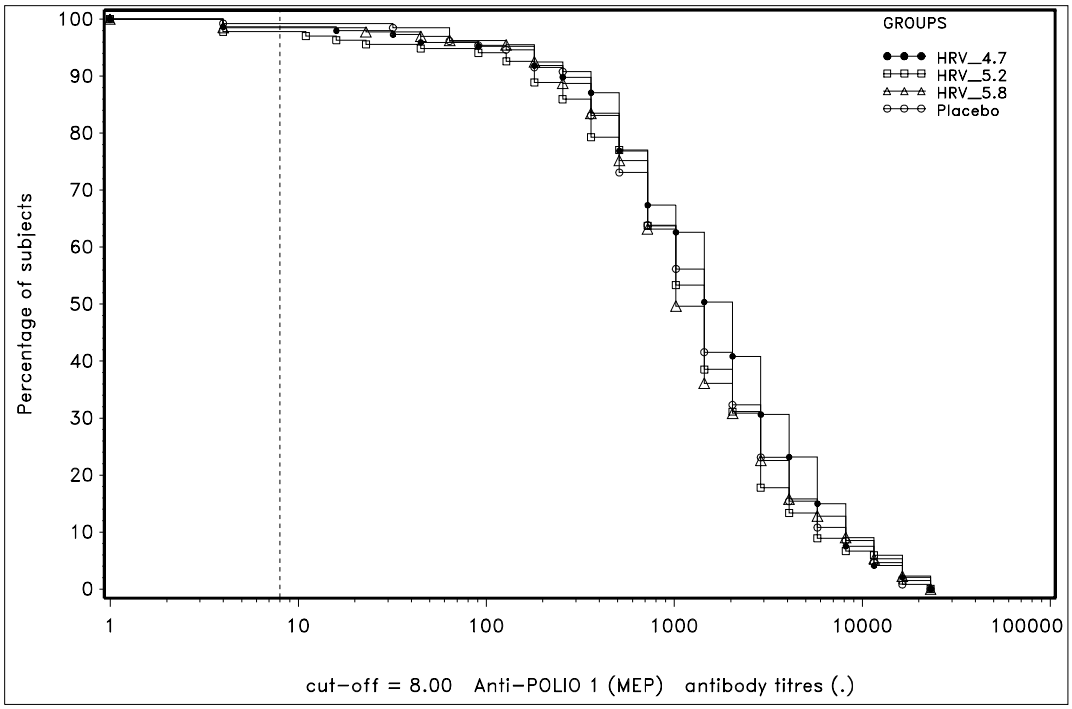
Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMT ratio is derived as the geometric mean of the 3 individual GMT ratios

Supplement 156: Ratio of anti-poliovirus type 3 antibody GMTs between pooled/each HRV vaccine groups and the placebo group at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)

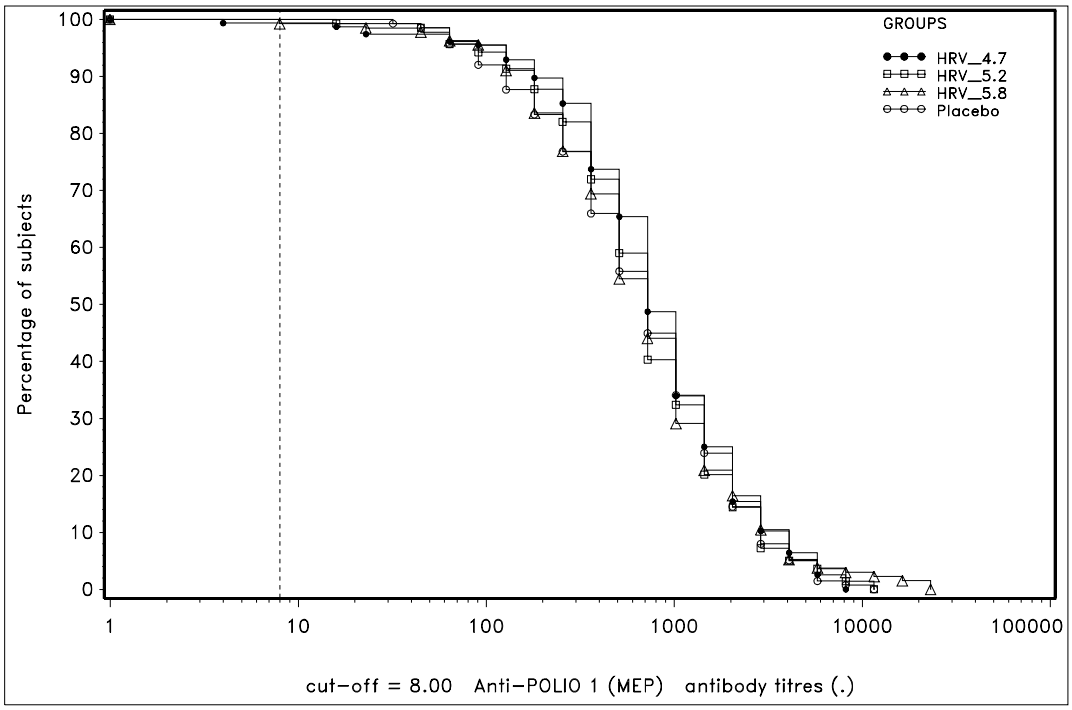
						GMC ratio			
							Value	95% CI	
Group	N	GMC	Group	N	GMC	Groups	%	LL	UL
Placebo	148	109.2	HRV _4.7	164	131.1	Placebo over HRV _4.7	0.83	0.61	1.14
			HRV _5.2	147	107.3	Placebo over HRV _5.2	1.02	0.74	1.40
			HRV _5.8	140	130.9	Placebo over HRV _5.8	0.83	0.60	1.16
						Placebo over Pooled HRV Groups*	0.89	0.68	1.16

Notes: N = number of subjects with available data
95%CI, LL, UL: 95% lower and upper confidence interval limits (Anova model – pooled variance with more than 2 groups)
* For the pooled HRV group, the GMT ratio is derived as the geometric mean of the 3 individual GMT ratios

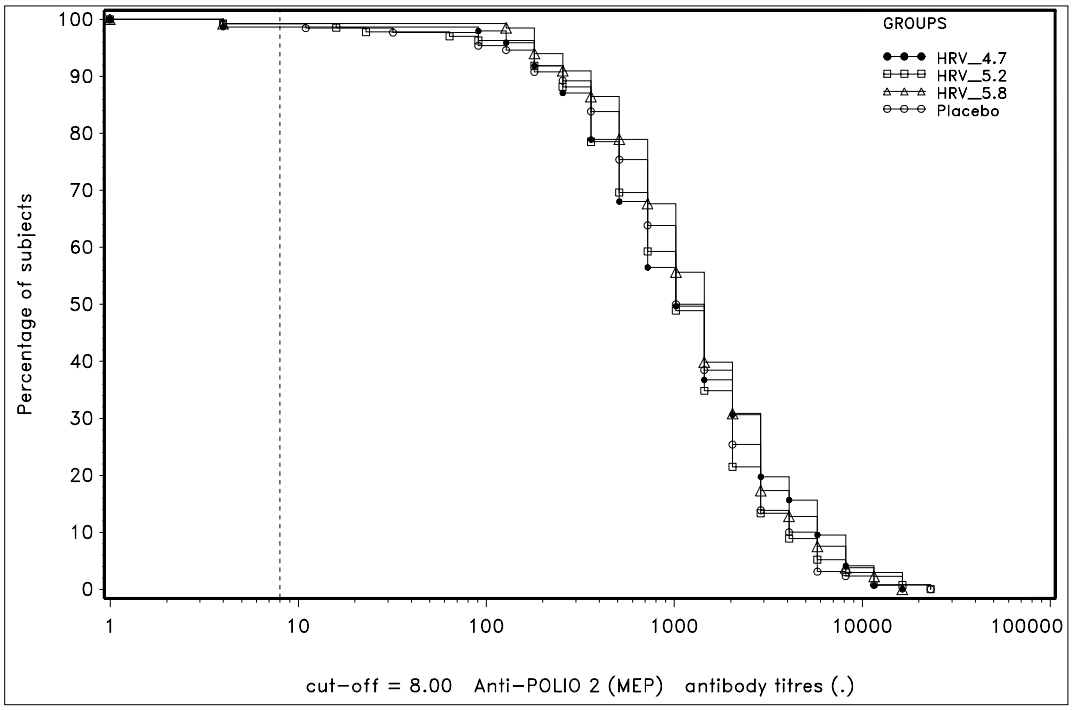
Supplement 157: Reverse cumulative curve for anti-poliovirus type 1 antibody titers at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



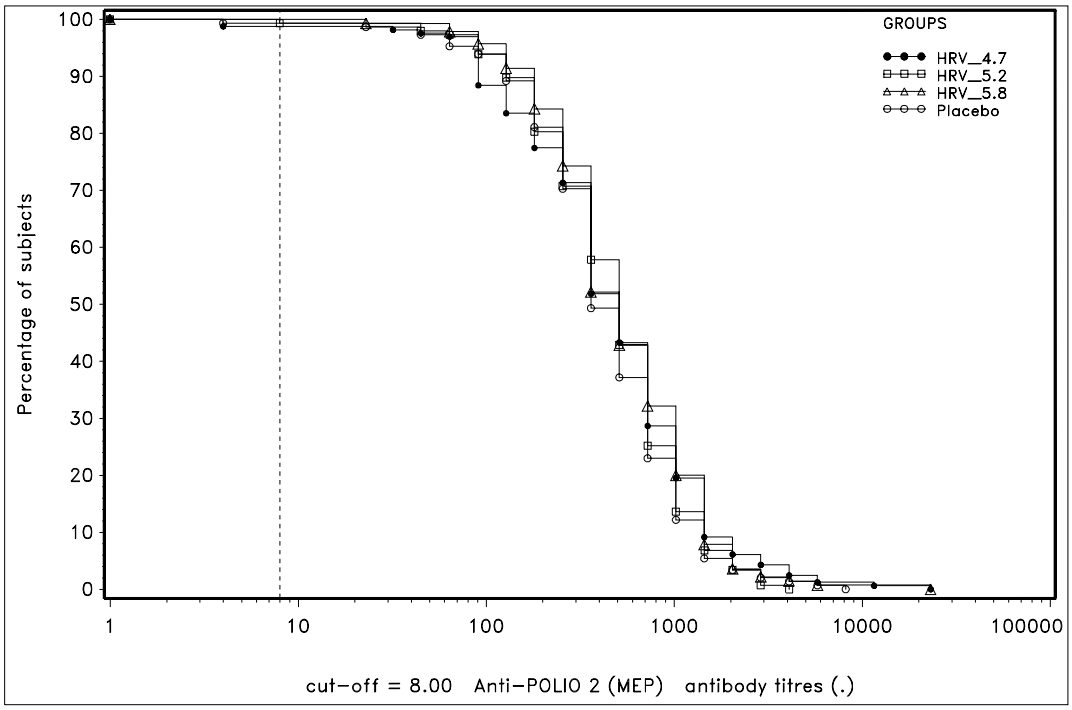
Supplement 158: Reverse cumulative curve for anti-poliovirus type 1 antibody titers at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



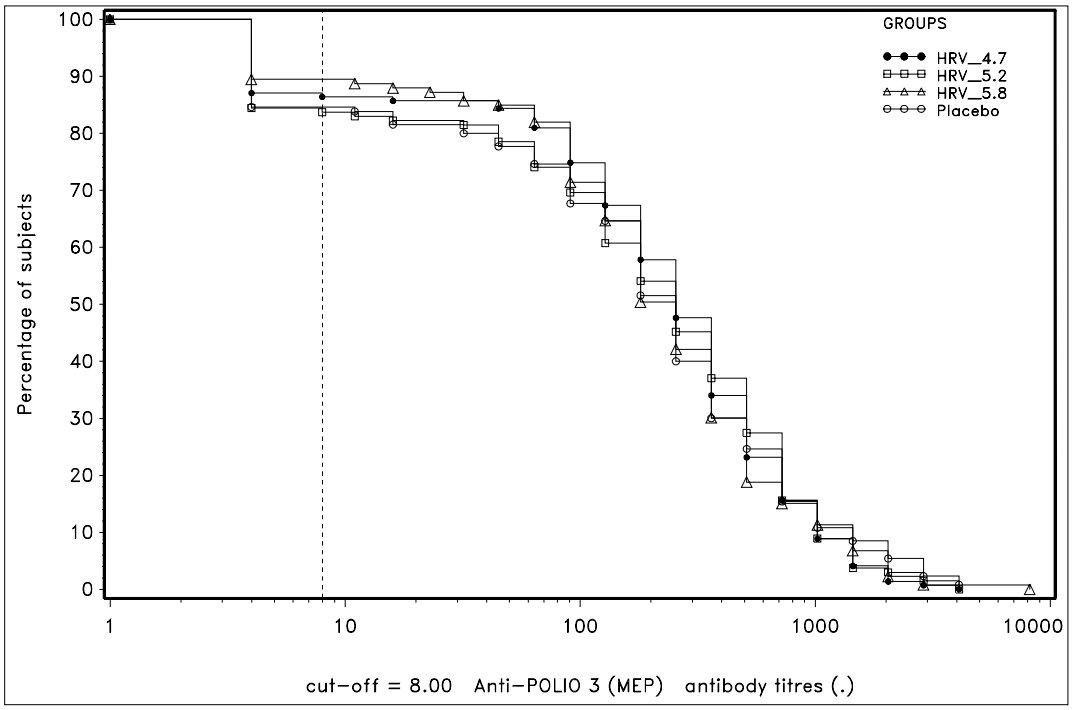
Supplement 159: Reverse cumulative curve for anti-poliovirus type 2 antibody titers at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



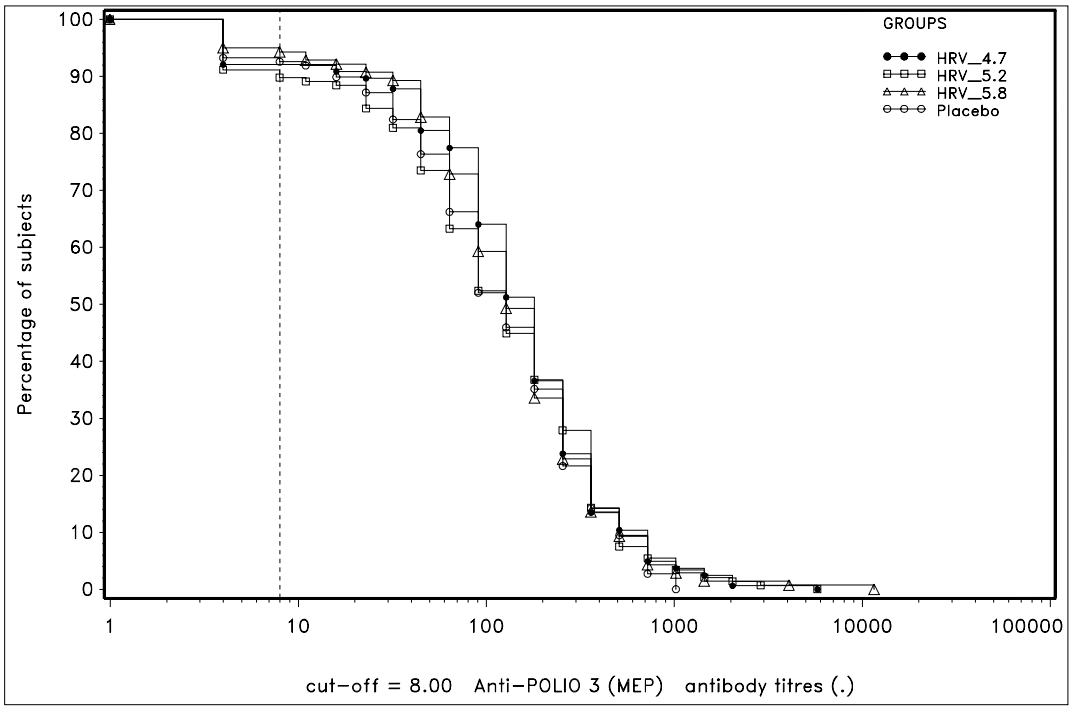
Supplement 160: Reverse cumulative curve for anti-poliovirus type 2 antibody titers at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 161: Reverse cumulative curve for anti-poliovirus type 3 antibody titers at two months after Dose 2 of HRV vaccine or placebo (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 162: Reverse cumulative curve for anti-poliovirus type 3 antibody titers at the end of the first efficacy period (ATP cohort for immunogenicity for subset planned to receive two doses of study vaccine)



Supplement 163: Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Antibody	Group	Timing	N	≥ 0.1 IU/ml				GMC		
						95% CI		Value	95% CI	
				n	%	LL	UL		LL	UL
Anti-Diphtheria	**HRV_4.7**	PII(M4)	187	121	64.7	57.4	71.5	0.201	0.167	0.242
		PII(M10)	209	144	68.9	62.1	75.1	0.189	0.163	0.219
	HRV_5.2	PII(M4)	180	104	57.8	50.2	65.1	0.176	0.144	0.215
		PII(M10)	203	140	69.0	62.1	75.3	0.191	0.164	0.222
	HRV_5.8	PII(M4)	180	124	68.9	61.6	75.6	0.207	0.172	0.248
		PII(M10)	206	149	72.3	65.7	78.3	0.183	0.159	0.211
	Pooled HRV groups	PII(M4)	547	349	63.8	59.6	67.8	0.194	0.174	0.217
		PII(M10)	618	433	70.1	66.3	73.7	0.188	0.172	0.204
	Placebo	PII(M4)	186	129	69.4	62.2	75.9	0.253	0.207	0.310
		PII(M10)	207	149	72.0	65.3	78.0	0.194	0.168	0.225
Anti-Tetanus	**HRV_4.7**	PII(M4)	188	184	97.9	94.6	99.4	1.027	0.877	1.201
		PII(M10)	211	211	100.0	98.3	100.0	1.219	1.110	1.338
	HRV_5.2	PII(M4)	180	179	99.4	96.9	100.0	1.107	0.945	1.297
		PII(M10)	204	202	99.0	96.5	99.9	1.119	1.008	1.242
	HRV_5.8	PII(M4)	181	178	98.3	95.2	99.7	1.046	0.893	1.224
		PII(M10)	207	206	99.5	97.3	100.0	1.136	1.022	1.263
	Pooled HRV groups	PII(M4)	549	541	98.5	97.1	99.4	1.059	0.967	1.159
		PII(M10)	622	619	99.5	98.6	99.9	1.158	1.092	1.227
	Placebo	PII(M4)	187	186	99.5	97.1	100.0	1.137	0.969	1.335
		PII(M10)	208	208	100.0	98.2	100.0	1.090	0.987	1.205

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = blood sample taken at the end of the first efficacy period

Supplement 164: Seropositivity rates and anti-BPT antibody GMCs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 15 EL.U/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PII(M4)	185	117	63.2	55.9	70.2	18.5	16.5	20.7
	PII(M10)	210	155	73.8	67.3	79.6	22.2	20.0	24.6
HRV_5.2	PII(M4)	177	104	58.8	51.1	66.1	18.4	16.3	20.9
	PII(M10)	205	155	75.6	69.1	81.3	23.0	20.6	25.8
HRV_5.8	PII(M4)	182	111	61.0	53.5	68.1	17.9	16.0	20.1
	PII(M10)	207	143	69.1	62.3	75.3	21.5	19.2	24.2
Pooled HRV groups	PII(M4)	544	332	61.0	56.8	65.1	18.3	17.1	19.6
	PII(M10)	622	453	72.8	69.2	76.3	22.2	20.9	23.7
Placebo	PII(M4)	182	109	59.9	52.4	67.1	17.6	15.6	19.8
	PII(M10)	207	147	71.0	64.3	77.1	21.9	19.5	24.6

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered seropositive level
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = blood sample taken at the end of the first efficacy period

Supplement 165: Seroprotection rates and anti-HBs antibody GMCs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 10 mIU/ml				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
HRV_4.7	PII(M4)	188	185	98.4	95.4	99.7	524.570	435.165	632.345
	PII(M10)	210	201	95.7	92.0	98.0	213.467	176.657	257.948
HRV_5.2	PII(M4)	180	178	98.9	96.0	99.9	568.009	462.879	697.017
	PII(M10)	204	196	96.1	92.4	98.3	200.809	166.402	242.330
HRV_5.8	PII(M4)	184	179	97.3	93.8	99.1	515.978	421.350	631.857
	PII(M10)	207	201	97.1	93.8	98.9	213.276	177.723	255.941
Pooled HRV groups	PII(M4)	552	542	98.2	96.7	99.1	535.402	477.887	599.838
	PII(M10)	621	598	96.3	94.5	97.6	209.161	187.908	232.817
Placebo	PII(M4)	186	183	98.4	95.4	99.7	630.142	515.361	770.488
	PII(M10)	208	203	97.6	94.5	99.2	235.141	197.582	279.839

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered protective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = blood sample taken at the end of the first efficacy period

Supplement 166: Seroprotection rates and anti-PRP antibody GMCs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Group	Timing	N	≥ 0.15 mcg/ml				≥ 1 mcg/ml				GMC		
					95% CI		n	%	95% CI		Value	95% CI	
			n	%	LL	UL			LL	UL		LL	UL
HRV_4.7	**PII(M4)**	184	184	100.0	98.0	100.0	175	95.1	90.9	97.7	6.128	5.193	7.231
	PII(M10)	210	209	99.5	97.4	100.0	196	93.3	89.1	96.3	3.878	3.450	4.358
HRV_5.2	**PII(M4)**	180	179	99.4	96.9	100.0	159	88.3	82.7	92.6	5.399	4.468	6.523
	PII(M10)	203	202	99.5	97.3	100.0	189	93.1	88.7	96.2	3.957	3.496	4.479
HRV_5.8	**PII(M4)**	183	181	98.9	96.1	99.9	167	91.3	86.2	94.9	4.634	3.899	5.507
	PII(M10)	207	207	100.0	98.2	100.0	192	92.8	88.3	95.9	3.718	3.301	4.188
Pooled HRV groups	**PII(M4)**	547	544	99.5	98.4	99.9	501	91.6	88.9	93.8	5.353	4.837	5.924
	PII(M10)	620	618	99.7	98.8	100.0	577	93.1	90.8	94.9	3.849	3.593	4.124
Placebo	**PII(M4)**	183	182	99.5	97.0	100.0	165	90.2	84.9	94.1	5.379	4.492	6.442
	PII(M10)	205	205	100.0	98.2	100.0	194	94.6	90.6	97.3	3.964	3.496	4.494

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered seroprotective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = blood sample taken at the end of the first efficacy period

Supplement 167: Seroprotection rates and anti-poliovirus types 1, 2 and 3 GMTs (total vaccinated cohort for immunogenicity for subset planned to receive two doses of study vaccine)

Antibody	Group	Timing	N	≥ 1:8 dilution				GMC		
						95% CI		Value	95% CI	
				n	%	LL	UL		LL	UL
Anti-Polio 1	HRV_4.7	PII(M4)	187	185	98.9	96.2	99.9	1536.6	1230.4	1919.0
		PII(M10)	199	197	99.0	96.4	99.9	788.7	665.6	934.6
	HRV_5.2	PII(M4)	178	173	97.2	93.6	99.1	1041.9	816.9	1329.0
		PII(M10)	190	189	99.5	97.1	100.0	703.3	590.0	838.3
	HRV_5.8	PII(M4)	183	180	98.4	95.3	99.7	1205.1	973.1	1492.5
		PII(M10)	190	189	99.5	97.1	100.0	663.4	551.0	798.8
	Pooled HRV groups	PII(M4)	548	538	98.2	96.7	99.1	1248.9	1095.9	1423.2
		PII(M10)	579	575	99.3	98.2	99.8	717.7	648.2	794.5
	Placebo	PII(M4)	183	181	98.9	96.1	99.9	1304.8	1059.8	1606.5
		PII(M10)	194	194	100.0	98.1	100.0	655.1	548.6	782.3
Anti-Polio 2	HRV_4.7	PII(M4)	187	184	98.4	95.4	99.7	1076.6	885.7	1308.5
		PII(M10)	209	207	99.0	96.6	99.9	465.2	397.2	544.9
	HRV_5.2	PII(M4)	179	175	97.8	94.4	99.4	964.4	783.2	1187.6
		PII(M10)	201	200	99.5	97.3	100.0	460.0	397.8	532.1
	HRV_5.8	PII(M4)	183	182	99.5	97.0	100.0	1211.8	1015.4	1446.2
		PII(M10)	204	203	99.5	97.3	100.0	497.5	433.2	571.4
	Pooled HRV groups	PII(M4)	549	541	98.5	97.1	99.4	1080.4	966.6	1207.7
		PII(M10)	614	610	99.3	98.3	99.8	474.0	435.4	516.0
	Placebo	PII(M4)	183	181	98.9	96.1	99.9	1029.7	854.6	1240.8
		PII(M10)	206	205	99.5	97.3	100.0	423.4	365.5	490.4
Anti-Polio 3	HRV_4.7	PII(M4)	187	159	85.0	79.1	89.8	165.3	126.8	215.6
		PII(M10)	209	192	91.9	87.3	95.2	121.9	100.7	147.4
	HRV_5.2	PII(M4)	179	151	84.4	78.2	89.3	145.2	109.2	193.1
		PII(M10)	201	183	91.0	86.2	94.6	102.2	83.0	125.8
	HRV_5.8	PII(M4)	183	158	86.3	80.5	91.0	159.8	123.1	207.5
		PII(M10)	204	192	94.1	90.0	96.9	113.6	94.1	137.2
	Pooled HRV groups	PII(M4)	549	468	85.2	82.0	88.1	156.7	134.1	183.0
		PII(M10)	614	567	92.3	90.0	94.3	112.4	100.4	125.8
	Placebo	PII(M4)	183	154	84.2	78.0	89.1	149.7	112.6	199.2
		PII(M10)	206	191	92.7	88.3	95.9	105.2	86.9	127.3

Notes: N = number of subjects with available results
n/% = number/percentage of subjects with concentration above the considered seroprotective level
95% CI = 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit
PII(M 4) = blood sample taken at two months after Dose 2
PII(M 10) = blood sample taken at the end of the first efficacy period

Supplement 168: Summary of demographic characteristics (age calculated in weeks) (total vaccinated cohort receiving three doses of study vaccine)

Characteristics	Parameters or Categories	HRV_4.7 N= 31		HRV_5.2 N= 30		HRV_5.8 N= 30	
		Value or n	%	Value or n	%	Value or n	%
Age at first Dose(weeks)	Mean	9.6	-	10.0	-	9.6	-
	SD	1.78	-	1.53	-	1.38	-
	Median	10	-	10	-	10	-
	Minimum	6	-	7	-	7	-
	Maximum	12	-	12	-	12	-
Gender	Female	21	67.7	10	33.3	10	33.3
	Male	10	32.3	20	66.7	20	66.7
Race	Black	1	3.2	1	3.3	1	3.3
	White/Caucasian	7	22.6	6	20.0	5	16.7
	Other	23	74.2	23	76.7	24	80.0
Height(cm)	Mean	56.8	-	57.1	-	57.7	-
	SD	2.29	-	3.17	-	2.47	-
	Median	57	-	57.5	-	58	-
Weight(kg)	Mean	5.4	-	5.8	-	5.7	-
	SD	0.63	-	0.97	-	0.79	-
	Median	5.4	-	5.6	-	5.55	-

Characteristics	Parameters or Categories	Placebo N= 30		Total N= 121	
		Value or n	%	Value or n	%
Age at first Dose(weeks)	Mean	10.1	-	9.8	-
	SD	1.53	-	1.60	-
	Median	11	-	10	-
	Minimum	6	-	6	-
	Maximum	12	-	12	-
Gender	Female	12	40.0	53	43.8
	Male	18	60.0	68	56.2
Race	Black	0	0.0	3	2.5
	White/Caucasian	6	20.0	24	19.8
	Other	24	80.0	94	77.7
Height(cm)	Mean	57.2	-	57.2	-
	SD	2.85	-	2.70	-
	Median	57	-	57	-
Weight(kg)	Mean	5.8	-	5.6	-
	SD	0.84	-	0.80	-
	Median	5.7	-	5.5	-

Notes: N = total number of subjects by group or in total (sum for all groups)
n/% = number/percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
Comment: Race "other" was reported as " Mestizo, Mestiza or Mixed"

Supplement 169: Increase in height and weight from Visit 1 to Visit 2, 3, 4 and 5 (total vaccinated cohort receiving three doses of study vaccine)

Visit	Characteristics	Parameters or Categories	HRV _4.7 N = (31)	HRV_5.2 N = (30)	HRV_5.8 N = (30)	Placebo N = (30)	Total N = (121)
			Value	Value	Value	Value	Value
Visit 2	Increase in height (cm) from Visit 1	Mean	6.2	6.0	5.0	5.6	5.7
		SD	2.67	2.86	3.01	1.81	2.63
		Median	6	6	5.5	5.5	6
		Unknown	1	0	0	0	1
	Increase in weight (kg) from Visit 1	Mean	1.5	1.5	1.5	1.4	1.5
		SD	0.4	0.55	0.41	0.49	0.46
		Median	1.5	1.4	1.4	1.4	1.4
		Unknown	0	0	0	0	0
Visit 3	Increase in height (cm) from Visit 1	Mean	10.5	10.5	9.8	10.1	10.2
		SD	2.96	3.36	2.71	1.68	2.73
		Median	10	10	11	10	10
		Unknown	1	0	0	1	2
	Increase in weight (kg) from Visit 1	Mean	2.4	2.4	2.4	2.5	2.4
		SD	0.7	0.64	0.55	0.74	0.66
		Median	2.5	2.4	2.1	2.4	2.4
		Unknown	0	0	1	0	1
Visit 4	Increase in height (cm) from Visit 1	Mean	13.1	13.1	12.8	13.0	13.0
		SD	3.96	3.11	3.93	2.31	3.36
		Median	12	13	13	13	12.5
		Unknown	0	0	1	0	1
	Increase in weight (kg) from Visit 1	Mean	3.0	2.9	2.9	3.1	3.0
		SD	0.61	0.74	0.73	0.7	0.69
		Median	2.9	2.9	2.8	3	2.9
		Unknown	0	0	1	0	1
Visit 5	Increase in height (cm) from Visit 1	Mean	17.5	16.9	16.5	16.6	16.9
		SD	3.31	3.2	3.76	2.68	3.24
		Median	18	17	17	17.5	17
		Unknown	0	1	0	0	1
	Increase in weight (kg) from Visit 1	Mean	4.0	3.6	3.9	3.9	3.9
		SD	0.65	0.82	0.94	0.93	0.85
		Median	4.1	3.6	3.75	3.85	3.85
		Unknown	0	1	0	0	1

Notes: N = total number of subjects by group or in total (sum of all groups)
value = value of the considered parameter
SD = standard deviation

Supplement 170: Summary of feeding criteria (total vaccinated cohort receiving three doses of study vaccine)

Dose	Group	N	Feeding criteria					
			Breast milk		Infant formula		Both	
			n	%	n	%	n	%
1	HRV_4.7	31	25	80.6	0	0.0	6	19.4
	HRV_5.2	30	21	70.0	0	0.0	9	30.0
	HRV_5.8	30	23	76.7	0	0.0	7	23.3
	Placebo	30	22	73.3	0	0.0	8	26.7
2	HRV_4.7	31	14	45.2	1	3.2	16	51.6
	HRV_5.2	30	17	56.7	1	3.3	12	40.0
	HRV_5.8	30	18	60.0	0	0.0	12	40.0
	Placebo	30	20	66.7	2	6.7	8	26.7
3	HRV_4.7	31	4	12.9	2	6.5	25	80.6
	HRV_5.2	30	5	16.7	3	10.0	22	73.3
	HRV_5.8	30	3	10.0	1	3.3	26	86.7
	Placebo	30	5	16.7	4	13.3	21	70.0

Notes: N = number of subjects having received the considered dose and with available data
n/% = number/percentage of subjects with the specified feeding criteria

Supplement 171: Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15 days follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	31	6	19.4	7.5	37.5
	HRV_5.2	30	6	20.0	7.7	38.6
	HRV_5.8	30	4	13.3	3.8	30.7
	Pooled HRV groups	91	16	17.6	10.4	27.0
	Placebo	30	7	23.3	9.9	42.3
Dose 2	**HRV_4.7**	31	9	29.0	14.2	48.0
	HRV_5.2	30	9	30.0	14.7	49.4
	HRV_5.8	30	5	16.7	5.6	34.7
	Pooled HRV groups	91	23	25.3	16.7	35.5
	Placebo	30	4	13.3	3.8	30.7
Dose 3	**HRV_4.7**	31	7	22.6	9.6	41.1
	HRV_5.2	30	6	20.0	7.7	38.6
	HRV_5.8	30	8	26.7	12.3	45.9
	Pooled HRV groups	91	21	23.1	14.9	33.1
	Placebo	30	7	23.3	9.9	42.3
Overall/dose	**HRV_4.7**	93	22	23.7	15.5	33.6
	HRV_5.2	90	21	23.3	15.1	33.4
	HRV_5.8	90	17	18.9	11.4	28.5
	Pooled HRV groups	273	60	22.0	17.2	27.4
	Placebo	90	18	20.0	12.3	29.8
Overall/subject	**HRV_4.7**	31	14	45.2	27.3	64.0
	HRV_5.2	30	13	43.3	25.5	62.6
	HRV_5.8	30	14	46.7	28.3	65.7
	Pooled HRV groups	91	41	45.1	34.6	55.8
	Placebo	30	14	46.7	28.3	65.7

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 172: Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15 days follow-up (total vaccinated cohort for safety receiving three doses of study vaccine)

		Symptoms				
		N	n	%	95% CI	
					LL	UL
Dose 1	**HRV_4.7**	31	29	93.5	78.6	99.2
	HRV_5.2	30	29	96.7	82.8	99.9
	HRV_5.8	30	28	93.3	77.9	99.2
	Pooled HRV groups	91	86	94.5	87.6	98.2
	Placebo	30	27	90.0	73.5	97.9
Dose 2	**HRV_4.7**	31	25	80.6	62.5	92.5
	HRV_5.2	30	21	70.0	50.6	85.3
	HRV_5.8	30	25	83.3	65.3	94.4
	Pooled HRV groups	91	71	78.0	68.1	86.0
	Placebo	30	28	93.3	77.9	99.2
Dose 3	**HRV_4.7**	31	28	90.3	74.2	98.0
	HRV_5.2	30	22	73.3	54.1	87.7
	HRV_5.8	30	24	80.0	61.4	92.3
	Pooled HRV groups	91	74	81.3	71.8	88.7
	Placebo	30	25	83.3	65.3	94.4
Overall/dose	**HRV_4.7**	93	82	88.2	79.8	93.9
	HRV_5.2	90	72	80.0	70.2	87.7
	HRV_5.8	90	77	85.6	76.6	92.1
	Pooled HRV groups	273	231	84.6	79.8	88.7
	Placebo	90	80	88.9	80.5	94.5
Overall/subject	**HRV_4.7**	31	31	100.0	88.8	100.0
	HRV_5.2	30	30	100.0	88.4	100.0
	HRV_5.8	30	29	96.7	82.8	99.9
	Pooled HRV groups	91	90	98.9	94.0	100.0
	Placebo	30	30	100.0	88.4	100.0

Notes: For each dose: N = number of subjects having received the considered dose
n/% = number/percentage of subjects reporting at least one symptom for the considered dose
For overall/dose: N = total number of doses administered
n/% = total number/percentage of doses reporting at least one symptom
For overall/subject: N= number of subjects having received at least one dose
n/% = number percentage of subjects reporting at least one symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 173: Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" and grade "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine)

Dose Group		Overall/dose											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		93				90				90			
COUGH	Total	64	68.8	58.4	78.0	72	80.0	70.2	87.7	72	80.0	70.2	87.7
	Grade 2*3	31	33.3	23.9	43.9	36	40.0	29.8	50.9	37	41.1	30.8	52.0
	Grade 3	8	8.6	3.8	16.2	12	13.3	7.1	22.1	6	6.7	2.5	13.9
	Related	30	32.3	22.9	42.7	33	36.7	26.8	47.5	33	36.7	26.8	47.5
DIARRHEA	Total	16	17.2	10.2	26.4	11	12.2	6.3	20.8	19	21.1	13.2	31.0
	Grade 2*3	11	11.8	6.1	20.2	4	4.4	1.2	11.0	14	15.6	8.8	24.7
	Grade 3	7	7.5	3.1	14.9	1	1.1	0.0	6.0	3	3.3	0.7	9.4
	Related	12	12.9	6.8	21.5	8	8.9	3.9	16.8	14	15.6	8.8	24.7
IRRITABILITY	Total	63	67.7	57.3	77.1	57	63.3	52.5	73.2	61	67.8	57.1	77.2
	Grade 2*3	38	40.9	30.8	51.5	40	44.4	34.0	55.3	38	42.2	31.9	53.1
	Grade 3	9	9.7	4.5	17.6	7	7.8	3.2	15.4	6	6.7	2.5	13.9
	Related	59	63.4	52.8	73.2	51	56.7	45.8	67.1	56	62.2	51.4	72.2
LOSS OF APPETITE	Total	31	33.3	23.9	43.9	30	33.3	23.7	44.1	28	31.1	21.8	41.7
	Grade 2*3	12	12.9	6.8	21.5	12	13.3	7.1	22.1	11	12.2	6.3	20.8
	Grade 3	2	2.2	0.3	7.6	2	2.2	0.3	7.8	2	2.2	0.3	7.8
	Related	20	21.5	13.7	31.2	22	24.4	16.0	34.6	26	28.9	19.8	39.4
FEVER	Total	61	65.6	55.0	75.1	49	54.4	43.6	65.0	52	57.8	46.9	68.1
	Grade 2*3	28	30.1	21.0	40.5	22	24.4	16.0	34.6	25	27.8	18.9	38.2
	Grade 3	3	3.2	0.7	9.1	2	2.2	0.3	7.8	3	3.3	0.7	9.4
	Related	58	62.4	51.7	72.2	43	47.8	37.1	58.6	48	53.3	42.5	63.9
VOMITING	Total	28	30.1	21.0	40.5	28	31.1	21.8	41.7	25	27.8	18.9	38.2
	Grade 2*3	14	15.1	8.5	24.0	14	15.6	8.8	24.7	10	11.1	5.5	19.5
	Grade 3	5	5.4	1.8	12.1	4	4.4	1.2	11.0	3	3.3	0.7	9.4
	Related	20	21.5	13.7	31.2	23	25.6	16.9	35.8	17	18.9	11.4	28.5

Notes: For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 173 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" and grade "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine)

Dose		Overall/dose							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		273				90			
COUGH	Total	208	76.2	70.7	81.1	64	71.1	60.6	80.2
	Grade 2*3	104	38.1	32.3	44.1	34	37.8	27.8	48.6
	Grade 3	26	9.5	6.3	13.6	6	6.7	2.5	13.9
	Related	96	35.2	29.5	41.1	35	38.9	28.8	49.7
DIARRHEA	Total	46	16.8	12.6	21.8	16	17.8	10.5	27.3
	Grade 2*3	29	10.6	7.2	14.9	9	10.0	4.7	18.1
	Grade 3	11	4.0	2.0	7.1	2	2.2	0.3	7.8
	Related	34	12.5	8.8	17.0	12	13.3	7.1	22.1
IRRITABILITY	Total	181	66.3	60.4	71.9	62	68.9	58.3	78.2
	Grade 2*3	116	42.5	36.6	48.6	39	43.3	32.9	54.2
	Grade 3	22	8.1	5.1	11.9	7	7.8	3.2	15.4
	Related	166	60.8	54.7	66.6	55	61.1	50.3	71.2
LOSS OF APPETITE	Total	89	32.6	27.1	38.5	30	33.3	23.7	44.1
	Grade 2*3	35	12.8	9.1	17.4	16	17.8	10.5	27.3
	Grade 3	6	2.2	0.8	4.7	1	1.1	0.0	6.0
	Related	68	24.9	19.9	30.5	23	25.6	16.9	35.8
FEVER	Total	162	59.3	53.3	65.2	46	51.1	40.3	61.8
	Grade 2*3	75	27.5	22.3	33.2	14	15.6	8.8	24.7
	Grade 3	8	2.9	1.3	5.7	1	1.1	0.0	6.0
	Related	149	54.6	48.5	60.6	40	44.4	34.0	55.3
VOMITING	Total	81	29.7	24.3	35.5	19	21.1	13.2	31.0
	Grade 2*3	38	13.9	10.0	18.6	12	13.3	7.1	22.1
	Grade 3	12	4.4	2.3	7.6	3	3.3	0.7	9.4
	Related	60	22.0	17.2	27.4	14	15.6	8.8	24.7

Notes: For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 173 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" and grade "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine)

Dose Group		Overall/subject											
		HRV_4.7				HRV_5.2				HRV_5.8			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
N		31				30				30			
COUGH	Total	28	90.3	74.2	98.0	28	93.3	77.9	99.2	29	96.7	82.8	99.9
	Grade 2*3	18	58.1	39.1	75.5	23	76.7	57.7	90.1	20	66.7	47.2	82.7
	Grade 3	5	16.1	5.5	33.7	9	30.0	14.7	49.4	4	13.3	3.8	30.7
	Related	21	67.7	48.6	83.3	19	63.3	43.9	80.1	21	70.0	50.6	85.3
DIARRHEA	Total	13	41.9	24.5	60.9	9	30.0	14.7	49.4	12	40.0	22.7	59.4
	Grade 2*3	9	29.0	14.2	48.0	4	13.3	3.8	30.7	11	36.7	19.9	56.1
	Grade 3	6	19.4	7.5	37.5	1	3.3	0.1	17.2	3	10.0	2.1	26.5
	Related	11	35.5	19.2	54.6	7	23.3	9.9	42.3	9	30.0	14.7	49.4
IRRITABILITY	Total	29	93.5	78.6	99.2	28	93.3	77.9	99.2	29	96.7	82.8	99.9
	Grade 2*3	21	67.7	48.6	83.3	24	80.0	61.4	92.3	22	73.3	54.1	87.7
	Grade 3	6	19.4	7.5	37.5	6	20.0	7.7	38.6	5	16.7	5.6	34.7
	Related	27	87.1	70.2	96.4	27	90.0	73.5	97.9	29	96.7	82.8	99.9
LOSS OF APPETITE	Total	17	54.8	36.0	72.7	19	63.3	43.9	80.1	19	63.3	43.9	80.1
	Grade 2*3	9	29.0	14.2	48.0	8	26.7	12.3	45.9	9	30.0	14.7	49.4
	Grade 3	2	6.5	0.8	21.4	2	6.7	0.8	22.1	2	6.7	0.8	22.1
	Related	15	48.4	30.2	66.9	16	53.3	34.3	71.7	19	63.3	43.9	80.1
FEVER	Total	30	96.8	83.3	99.9	27	90.0	73.5	97.9	26	86.7	69.3	96.2
	Grade 2*3	17	54.8	36.0	72.7	13	43.3	25.5	62.6	16	53.3	34.3	71.7
	Grade 3	2	6.5	0.8	21.4	2	6.7	0.8	22.1	3	10.0	2.1	26.5
	Related	30	96.8	83.3	99.9	25	83.3	65.3	94.4	26	86.7	69.3	96.2
VOMITING	Total	17	54.8	36.0	72.7	19	63.3	43.9	80.1	15	50.0	31.3	68.7
	Grade 2*3	10	32.3	16.7	51.4	10	33.3	17.3	52.8	8	26.7	12.3	45.9
	Grade 3	4	12.9	3.6	29.8	4	13.3	3.8	30.7	3	10.0	2.1	26.5
	Related	14	45.2	27.3	64.0	18	60.0	40.6	77.3	11	36.7	19.9	56.1

Notes: For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 173 (continued): Percentage of doses and of subjects reporting each solicited general symptoms included those graded "3" and grade "2" or "3" in intensity and those considered to be related to vaccination, during the solicited 15 day follow-up period (total vaccinated cohort for safety receiving three doses of study vaccine)

Dose		Overall/subject							
Group		Pooled HRV groups				Placebo			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
N		91				30			
COUGH	Total	85	93.4	86.2	97.5	28	93.3	77.9	99.2
	Grade 2*3	61	67.0	56.4	76.5	19	63.3	43.9	80.1
	Grade 3	18	19.8	12.2	29.4	5	16.7	5.6	34.7
	Related	61	67.0	56.4	76.5	22	73.3	54.1	87.7
DIARRHEA	Total	34	37.4	27.4	48.1	12	40.0	22.7	59.4
	Grade 2*3	24	26.4	17.7	36.7	8	26.7	12.3	45.9
	Grade 3	10	11.0	5.4	19.3	2	6.7	0.8	22.1
	Related	27	29.7	20.5	40.2	9	30.0	14.7	49.4
IRRITABILITY	Total	86	94.5	87.6	98.2	28	93.3	77.9	99.2
	Grade 2*3	67	73.6	63.3	82.3	23	76.7	57.7	90.1
	Grade 3	17	18.7	11.3	28.2	6	20.0	7.7	38.6
	Related	83	91.2	83.4	96.1	27	90.0	73.5	97.9
LOSS OF APPETITE	Total	55	60.4	49.6	70.5	19	63.3	43.9	80.1
	Grade 2*3	26	28.6	19.6	39.0	12	40.0	22.7	59.4
	Grade 3	6	6.6	2.5	13.8	1	3.3	0.1	17.2
	Related	50	54.9	44.2	65.4	18	60.0	40.6	77.3
FEVER	Total	83	91.2	83.4	96.1	28	93.3	77.9	99.2
	Grade 2*3	46	50.5	39.9	61.2	14	46.7	28.3	65.7
	Grade 3	7	7.7	3.1	15.2	1	3.3	0.1	17.2
	Related	81	89.0	80.7	94.6	27	90.0	73.5	97.9
VOMITING	Total	51	56.0	45.2	66.4	12	40.0	22.7	59.4
	Grade 2*3	28	30.8	21.5	41.3	8	26.7	12.3	45.9
	Grade 3	11	12.1	6.2	20.6	3	10.0	2.1	26.5
	Related	43	47.3	36.7	58.0	10	33.3	17.3	52.8

Notes: For overall/dose: N = total number of doses administered
n/% = total number of doses reporting the specified symptom
For overall/subject: N = total number of subjects having received at least one dose
n/% = number/percentage of subjects reporting the specified symptom
Total = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 174: Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 31				HRV_5.2 N = 30				HRV_5.8 N = 30				Pooled HRV groups N = 91				Placebo N = 30			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
At least one symptom		28	90.3	74.2	98	29	96.7	82.8	99.9	30	100	88.4	100	87	95.6	89.1	98.8	30	100	88.4	100
Application site (1820)	Injection site reaction (0058)	2	6.5	0.8	21.4	1	3.3	0.1	17.2	1	3.3	0.1	17.2	4	4.4	1.2	10.9	3	10	2.1	26.5
	Otitis externa (0059)	1	3.2	0.1	16.7	0	0	0	11.6	0	0	0	11.6	1	1.1	0	6	0	0	0	11.6
Body as a whole general (1810)	Allergy (1058)	4	12.9	3.6	29.8	2	6.7	0.8	22.1	2	6.7	0.8	22.1	8	8.8	3.9	16.6	3	10	2.1	26.5
	Fever (0725)	9	29	14.2	48	11	36.7	19.9	56.1	9	30	14.7	49.4	29	31.9	22.5	42.5	14	46.7	28.3	65.7
	Injury (9001)	0	0	0	11.2	0	0	0	11.6	0	0	0	11.6	0	0	0	4	1	3.3	0.1	17.2
Central and peripheral nervous system (410)	Headache (0109)	0	0	0	11.2	1	3.3	0.1	17.2	0	0	0	11.6	1	1.1	0	6	0	0	0	11.6
Gastrointestinal system (600)	Abdominal pain (0268)	0	0	0	11.2	0	0	0	11.6	1	3.3	0.1	17.2	1	1.1	0	6	1	3.3	0.1	17.2
	Anorexia (0165)	1	3.2	0.1	16.7	1	3.3	0.1	17.2	2	6.7	0.8	22.1	4	4.4	1.2	10.9	2	6.7	0.8	22.1
	Constipation (0204)	0	0	0	11.2	1	3.3	0.1	17.2	2	6.7	0.8	22.1	3	3.3	0.7	9.3	1	3.3	0.1	17.2
	Gastroenteritis (0293)	1	3.2	0.1	16.7	0	0	0	11.6	2	6.7	0.8	22.1	3	3.3	0.7	9.3	3	10	2.1	26.5
	Gastrointestinal disorder nos (1262)	0	0	0	11.2	1	3.3	0.1	17.2	1	3.3	0.1	17.2	2	2.2	0.3	7.7	0	0	0	11.6
	Stomatitis (0327)	0	0	0	11.2	0	0	0	11.6	1	3.3	0.1	17.2	1	1.1	0	6	1	3.3	0.1	17.2
	Vomiting (0228)	4	12.9	3.6	29.8	4	13.3	3.8	30.7	6	20	7.7	38.6	14	15.4	8.7	24.5	3	10	2.1	26.5
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	11.2	0	0	0	11.6	0	0	0	11.6	0	0	0	4	1	3.3	0.1	17.2
	Earache (0260)	1	3.2	0.1	16.7	0	0	0	11.6	0	0	0	11.6	1	1.1	0	6	1	3.3	0.1	17.2
Psychiatric (500)	Nervousness (0188)	0	0	0	11.2	1	3.3	0.1	17.2	0	0	0	11.6	1	1.1	0	6	0	0	0	11.6

Notes: N = number of subjects having received at least one dose
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
At least one symptom = number of subjects reporting at least one unsolicited symptom, whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 174 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 31				HRV_5.2 N = 30				HRV_5.8 N = 30				Pooled HRV groups N = 91				Placebo N = 30			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Red blood cell (1210)	Anemia (0544)	0	0	0	11.2	1	3.3	0.1	17.2	0	0	0	11.6	1	1.1	0	6	1	3.3	0.1	17.2
Resistance mechanism (1830)	Abscess (0887)	0	0	0	11.2	0	0	0	11.6	1	3.3	0.1	17.2	1	1.1	0	6	0	0	0	11.6
	Infection (0736)	4	12.9	3.6	29.8	3	10	2.1	26.5	5	16.7	5.6	34.7	12	13.2	7	21.9	7	23.3	9.9	42.3
	Infection viral (0740)	26	83.9	66.3	94.5	19	63.3	43.9	80.1	22	73.3	54.1	87.7	67	73.6	63.3	82.3	27	90	73.5	97.9
	Moniliasis (0741)	1	3.2	0.1	16.7	0	0	0	11.6	2	6.7	0.8	22.1	3	3.3	0.7	9.3	1	3.3	0.1	17.2
	Otitis media (0750)	0	0	0	11.2	2	6.7	0.8	22.1	2	6.7	0.8	22.1	4	4.4	1.2	10.9	1	3.3	0.1	17.2
	Upper resp tract infection(0543)	6	19.4	7.5	37.5	11	36.7	19.9	56.1	5	16.7	5.6	34.7	22	24.2	15.8	34.3	2	6.7	0.8	22.1
Respiratory system (1100)	Asthma (1367)	1	3.2	0.1	16.7	0	0	0	11.6	0	0	0	11.6	1	1.1	0	6	1	3.3	0.1	17.2
	Bronchitis (0805)	6	19.4	7.5	37.5	5	16.7	5.6	34.7	6	20	7.7	38.6	17	18.7	11.3	28.2	5	16.7	5.6	34.7
	Coughing (0513)	9	29	14.2	48	9	30	14.7	49.4	6	20	7.7	38.6	24	26.4	17.7	36.7	9	30	14.7	49.4
	Pharyngitis (0523)	2	6.5	0.8	21.4	1	3.3	0.1	17.2	1	3.3	0.1	17.2	4	4.4	1.2	10.9	4	13.3	3.8	30.7
	Pneumonia (0528)	1	3.2	0.1	16.7	5	16.7	5.6	34.7	0	0	0	11.6	6	6.6	2.5	13.8	1	3.3	0.1	17.2
	Rhinitis (0539)	3	9.7	2	25.8	2	6.7	0.8	22.1	4	13.3	3.8	30.7	9	9.9	4.6	17.9	3	10	2.1	26.5
	Sputum increased (0541)	0	0	0	11.2	0	0	0	11.6	0	0	0	11.6	0	0	0	4	1	3.3	0.1	17.2
	Stridor (0542)	0	0	0	11.2	0	0	0	11.6	1	3.3	0.1	17.2	1	1.1	0	6	0	0	0	11.6

Notes: N = number of subjects having received at least one dose
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 174 (continued): Percentage of subjects with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 N = 31				HRV_5.2 N = 30				HRV_5.8 N = 30				Pooled HRV groups N = 91				Placebo N = 30			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL	s	%	LL	UL
Skin and appendages (100)	Dermatitis (0007)	0	0	0	11.2	2	6.7	0.8	22.1	1	3.3	0.1	17.2	3	3.3	0.7	9.3	0	0	0	11.6
	Furunculosis (0016)	1	3.2	0.1	16.7	2	6.7	0.8	22.1	2	6.7	0.8	22.1	5	5.5	1.8	12.4	3	10	2.1	26.5
	Pruritus (0024)	0	0	0	11.2	2	6.7	0.8	22.1	0	0	0	11.6	2	2.2	0.3	7.7	1	3.3	0.1	17.2
	Rash erythematous (0028)	0	0	0	11.2	0	0	0	11.6	1	3.3	0.1	17.2	1	1.1	0	6	0	0	0	11.6
	Rash pustular (0032)	0	0	0	11.2	2	6.7	0.8	22.1	2	6.7	0.8	22.1	4	4.4	1.2	10.9	0	0	0	11.6
	Skin disorder (0037)	3	9.7	2	25.8	1	3.3	0.1	17.2	3	10	2.1	26.5	7	7.7	3.1	15.2	4	13.3	3.8	30.7
	Sweat gland disorder(1166)	0	0	0	11.2	2	6.7	0.8	22.1	2	6.7	0.8	22.1	4	4.4	1.2	10.9	0	0	0	11.6
Urinary system (1300)	Dysuria (0601)	0	0	0	11.2	0	0	0	11.6	1	3.3	0.1	17.2	1	1.1	0	6	0	0	0	11.6
	Urinary retention (0157)	0	0	0	11.2	0	0	0	11.6	0	0	0	11.6	0	0	0	4	1	3.3	0.1	17.2
	Urinary tract infection (0628)	0	0	0	11.2	0	0	0	11.6	0	0	0	11.6	0	0	0	4	1	3.3	0.1	17.2
Vision (431)	Conjunctivitis (0238)	0	0	0	11.2	3	10	2.1	26.5	1	3.3	0.1	17.2	4	4.4	1.2	10.9	3	10	2.1	26.5

Notes: N = number of subjects having received at least one dose
s/% = number/percentage of subjects reporting at least once a specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 175: Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 93				HRV_5.2 D = 90				HRV_5.8 D = 90				Pooled HRV groups D = 273				Placebo D = 90			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		64	68.8	58.4	78	74	82.2	72.7	89.5	64	71.1	60.6	80.2	202	74	68.4	79.1	70	77.8	67.8	85.9
Application site (1820)	Injection site reaction (0058)	2	2.2	0.3	7.6	1	1.1	0	6	1	1.1	0	6	4	1.5	0.4	3.7	4	4.4	1.2	11
	Otitis externa (0059)	1	1.1	0	5.8	0	0	0	4	0	0	0	4	1	0.4	0	2	0	0	0	4
Body as a whole general (1810)	Allergy (1058)	5	5.4	1.8	12.1	2	2.2	0.3	7.8	3	3.3	0.7	9.4	10	3.7	1.8	6.6	4	4.4	1.2	11
	Fever (0725)	11	11.8	6.1	20.2	13	14.4	7.9	23.4	10	11.1	5.5	19.5	34	12.5	8.8	17	14	15.6	8.8	24.7
	Injury (9001)	0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6
Central and peripheral nervous system (410)	Headache (0109)	0	0	0	3.9	1	1.1	0	6	0	0	0	4	1	0.4	0	2	0	0	0	4
Gastrointestinal system (600)	Abdominal pain (0268)	0	0	0	3.9	0	0	0	4	1	1.1	0	6	1	0.4	0	2	1	1.1	0	6
	Anorexia (0165)	1	1.1	0	5.8	1	1.1	0	6	2	2.2	0.3	7.8	4	1.5	0.4	3.7	3	3.3	0.7	9.4
	Constipation (0204)	0	0	0	3.9	1	1.1	0	6	2	2.2	0.3	7.8	3	1.1	0.2	3.2	1	1.1	0	6
	Gastroenteritis (0293)	1	1.1	0	5.8	0	0	0	4	2	2.2	0.3	7.8	3	1.1	0.2	3.2	3	3.3	0.7	9.4
	Gastrointestinal disorder nos (1262)	0	0	0	3.9	1	1.1	0	6	1	1.1	0	6	2	0.7	0.1	2.6	0	0	0	4
	Stomatitis (0327)	0	0	0	3.9	0	0	0	4	1	1.1	0	6	1	0.4	0	2	1	1.1	0	6
	Vomiting (0228)	4	4.3	1.2	10.6	6	6.7	2.5	13.9	8	8.9	3.9	16.8	18	6.6	4	10.2	3	3.3	0.7	9.4

Supplement 175 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 93				HRV_5.2 D = 90				HRV_5.8 D = 90				Pooled HRV groups D = 273				Placebo D = 90			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Hearing and vestibular (432)	Ear disorder nos (1255)	0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6
	Earache (0260)	1	1.1	0	5.8	0	0	0	4	0	0	0	4	1	0.4	0	2	1	1.1	0	6
Psychiatric (500)	Nervousness (0188)	0	0	0	3.9	1	1.1	0	6	0	0	0	4	1	0.4	0	2	0	0	0	4
Red blood cell (1210)	Anemia (0544)	0	0	0	3.9	1	1.1	0	6	0	0	0	4	1	0.4	0	2	1	1.1	0	6
Resistance mechanism (1830)	Abscess (0887)	0	0	0	3.9	0	0	0	4	1	1.1	0	6	1	0.4	0	2	0	0	0	4
	Infection (0736)	4	4.3	1.2	10.6	4	4.4	1.2	11	6	6.7	2.5	13.9	14	5.1	2.8	8.5	9	10	4.7	18.1
	Infection viral (0740)	41	44.1	33.8	54.8	37	41.1	30.8	52	34	37.8	27.8	48.6	112	41	35.1	47.1	39	43.3	32.9	54.2
	Moniliasis (0741)	1	1.1	0	5.8	0	0	0	4	2	2.2	0.3	7.8	3	1.1	0.2	3.2	1	1.1	0	6
	Otitis media (0750)	0	0	0	3.9	3	3.3	0.7	9.4	2	2.2	0.3	7.8	5	1.8	0.6	4.2	1	1.1	0	6
	Upper resp tract infection (0543)	8	8.6	3.8	16.2	12	13.3	7.1	22.1	7	7.8	3.2	15.4	27	9.9	6.6	14.1	2	2.2	0.3	7.8
Respiratory system (1100)	Asthma (1367)	1	1.1	0	5.8	0	0	0	4	0	0	0	4	1	0.4	0	2	1	1.1	0	6
	Bronchitis (0805)	6	6.5	2.4	13.5	5	5.6	1.8	12.5	8	8.9	3.9	16.8	19	7	4.2	10.7	5	5.6	1.8	12.5
	Coughing (0513)	10	10.8	5.3	18.9	10	11.1	5.5	19.5	6	6.7	2.5	13.9	26	9.5	6.3	13.6	13	14.4	7.9	23.4
	Pharyngitis (0523)	2	2.2	0.3	7.6	1	1.1	0	6	1	1.1	0	6	4	1.5	0.4	3.7	5	5.6	1.8	12.5
	Pneumonia (0528)	1	1.1	0	5.8	5	5.6	1.8	12.5	0	0	0	4	6	2.2	0.8	4.7	1	1.1	0	6
	Rhinitis (0539)	3	3.2	0.7	9.1	2	2.2	0.3	7.8	5	5.6	1.8	12.5	10	3.7	1.8	6.6	3	3.3	0.7	9.4
	Sputum increased (0541)	0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6
	Stridor (0542)	0	0	0	3.9	0	0	0	4	1	1.1	0	6	1	0.4	0	2	0	0	0	4

Notes: D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 175 (continued): Percentage of doses with unsolicited symptoms classified by WHO preferred term from Day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 93				HRV_5.2 D = 90				HRV_5.8 D = 90				Pooled HRV groups D = 273				Placebo D = 90			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
Skin and appendages (100)	Dermatitis (0007)	0	0	0	3.9	2	2.2	0.3	7.8	1	1.1	0	6	3	1.1	0.2	3.2	0	0	0	4
	Furunculosis (0016)	1	1.1	0	5.8	2	2.2	0.3	7.8	3	3.3	0.7	9.4	6	2.2	0.8	4.7	3	3.3	0.7	9.4
	Pruritus (0024)	0	0	0	3.9	3	3.3	0.7	9.4	0	0	0	4	3	1.1	0.2	3.2	1	1.1	0	6
	Rash erythematous (0028)	0	0	0	3.9	0	0	0	4	1	1.1	0	6	1	0.4	0	2	0	0	0	4
	Rash pustular (0032)	0	0	0	3.9	2	2.2	0.3	7.8	2	2.2	0.3	7.8	4	1.5	0.4	3.7	0	0	0	4
	Skin disorder (0037)	3	3.2	0.7	9.1	1	1.1	0	6	3	3.3	0.7	9.4	7	2.6	1	5.2	5	5.6	1.8	12.5
	Sweat gland disorder (1166)	0	0	0	3.9	2	2.2	0.3	7.8	2	2.2	0.3	7.8	4	1.5	0.4	3.7	0	0	0	4
Urinary system (1300)	Dysuria (0601)	0	0	0	3.9	0	0	0	4	1	1.1	0	6	1	0.4	0	2	0	0	0	4
	Urinary retention (0157)	0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6
	Urinary tract infection (0628)	0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6
Vision (431)	Conjunctivitis (0238)	0	0	0	3.9	3	3.3	0.7	9.4	1	1.1	0	6	4	1.5	0.4	3.7	3	3.3	0.7	9.4

Notes: D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 176: Percentage of doses with unsolicited symptoms classified by WHO preferred term assessed as related to vaccination, from day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 93				HRV_5.2 D = 90				HRV_5.8 D = 90				Pooled HRV groups D = 273				Placebo D = 90			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6
Respiratory system (1100)	Pneumonia (0528)	0	0	0	3.9	0	0	0	4	0	0	0	4	0	0	0	1.3	1	1.1	0	6

Notes: D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 177: Percentage of doses with unsolicited symptoms classified by WHO preferred term with grade "3" from day 0 to Day 42 after any vaccination (total vaccinated cohort for safety receiving three doses of study vaccine)

WHO Body System (CODE)	WHO Preferred term (CODE)	HRV_4.7 D = 93				HRV_5.2 D = 90				HRV_5.8 D = 90				Pooled HRV groups D = 273				Placebo D = 90			
				95% CI				95% CI				95% CI				95% CI				95% CI	
		d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL	d	%	LL	UL
At least one symptom		1	1.1	0	5.8	4	4.4	1.2	11	2	2.2	0.3	7.8	7	2.6	1	5.2	4	4.4	1.2	11
Gastrointestinal system (600)	Gastroenteritis (0293)	1	1.1	0	5.8	0	0	0	4	2	2.2	0.3	7.8	3	1.1	0.2	3.2	3	3.3	0.7	9.4
Respiratory system (1100)	Pneumonia (0528)	0	0	0	3.9	4	4.4	1.2	11	0	0	0	4	4	1.5	0.4	3.7	1	1.1	0	6

Notes: D = Total number of doses administered
d/% = number/percentage of doses followed by at least one report of the specified unsolicited symptom
At least one symptom = number of doses followed by at least one report of an unsolicited symptom whatever the WHO preferred terms
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

Supplement 178: Number and percentage of doses and subjects who took at least one concomitant medication from Day 0 to Day 14 after vaccination by type (total vaccinated cohort for safety receiving three doses of study vaccine)

	Overall/dose											
	HRV_4.7 (N=93)				HRV_5.2 (N=90)				HRV_5.8 (N=90)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL				
Any medication	51	54.8	44.2	65.2	43	47.8	37.1	58.6	57	63.3	52.5	73.2
Any antipyretic	48	51.6	41.0	62.1	41	45.6	35.0	56.4	54	60.0	49.1	70.2
Prophylactic antipyretic	0	0.0	0.0	3.9	0	0.0	0.0	4.0	0	0.0	0.0	4.0
Any antibiotic	6	6.5	2.4	13.5	4	4.4	1.2	11.0	3	3.3	0.7	9.4

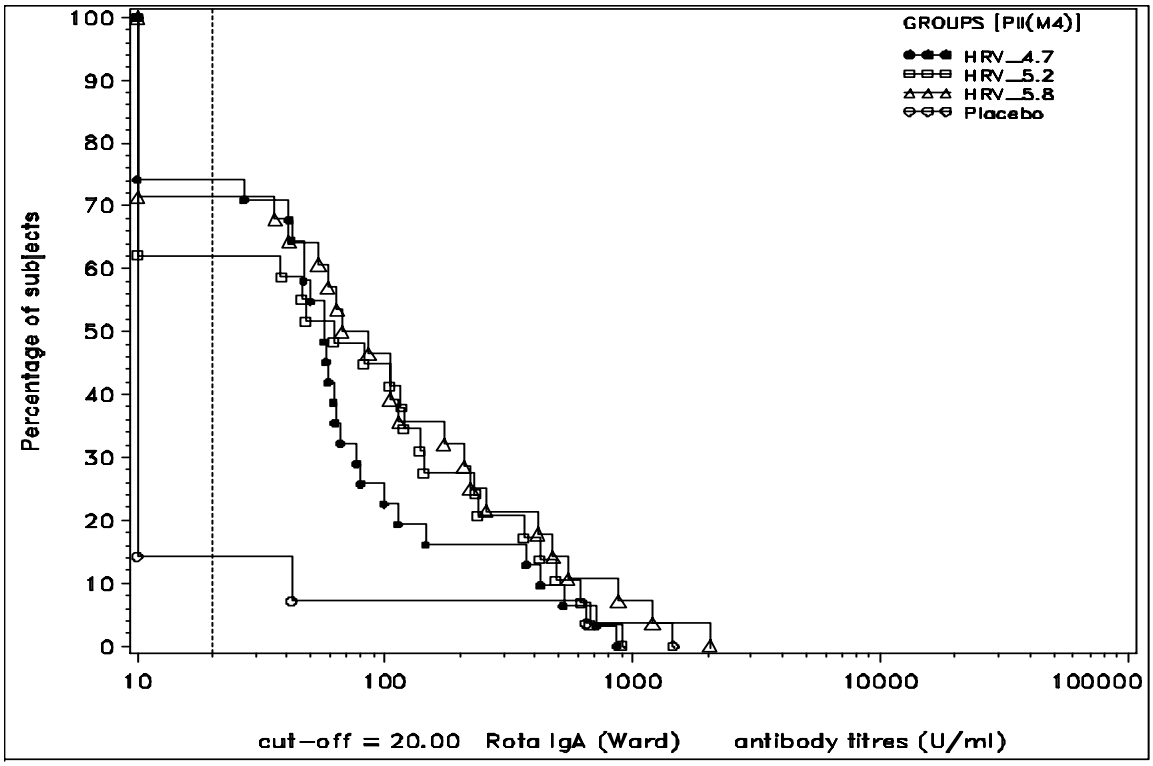
	Pooled HRV groups (N=273)				Placebo (N=90)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL
Any medication	151	55.3	49.2	61.3	46	51.1	40.3	61.8
Any antipyretic	143	52.4	46.3	58.4	45	50.0	39.3	60.7
Prophylactic antipyretic	0	0.0	0.0	1.3	1	1.1	0.0	6.0
Any antibiotic	13	4.8	2.6	8.0	3	3.3	0.7	9.4

	Overall/subject											
	HRV_4.7 (N=31)				HRV_5.2 (N=30)				HRV_5.8 (N=30)			
	n	%	95% CI		n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL				
Any medication	25	80.6	62.5	92.5	24	80.0	61.4	92.3	29	96.7	82.8	99.9
Any antipyretic	25	80.6	62.5	92.5	23	76.7	57.7	90.1	29	96.7	82.8	99.9
Prophylactic antipyretic	0	0.0	0.0	11.2	0	0.0	0.0	11.6	0	0.0	0.0	11.6
Any antibiotic	6	19.4	7.5	37.5	3	10.0	2.1	26.5	3	10.0	2.1	26.5

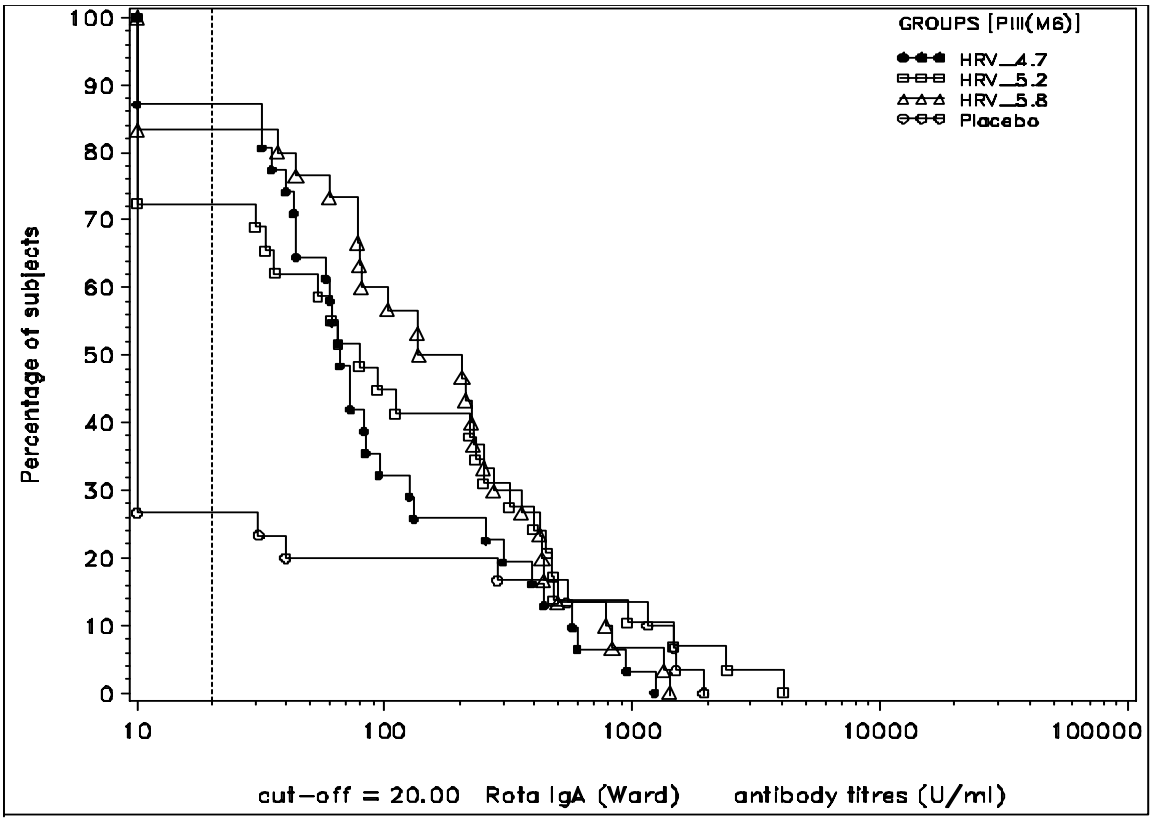
	Pooled HRV groups (N=91)				Placebo (N=30)			
	n	%	95% CI		n	%	95% CI	
Type			LL	UL			LL	UL
Any medication	78	85.7	76.8	92.2	24	80.0	61.4	92.3
Any antipyretic	77	84.6	75.5	91.3	24	80.0	61.4	92.3
Prophylactic antipyretic	0	0.0	0.0	4.0	1	3.3	0.1	17.2
Any antibiotic	12	13.2	7.0	21.9	3	10.0	2.1	26.5

Notes: For Overall/dose: N= total number of doses administered
n/% = number/percentage of doses with at least one specified concomitant medication, from Day 0 to Day 14.
For Overall/subject: N= total number of subjects having received at least one dose
n/% = total number/percentage of subject having who started taking the specified concomitant medication at least once after the considered dose, from Day 0 to Day 14
95% CI = exact 95% Confidence Interval; L.L. = Lower Limit, U.L. = Upper Limit

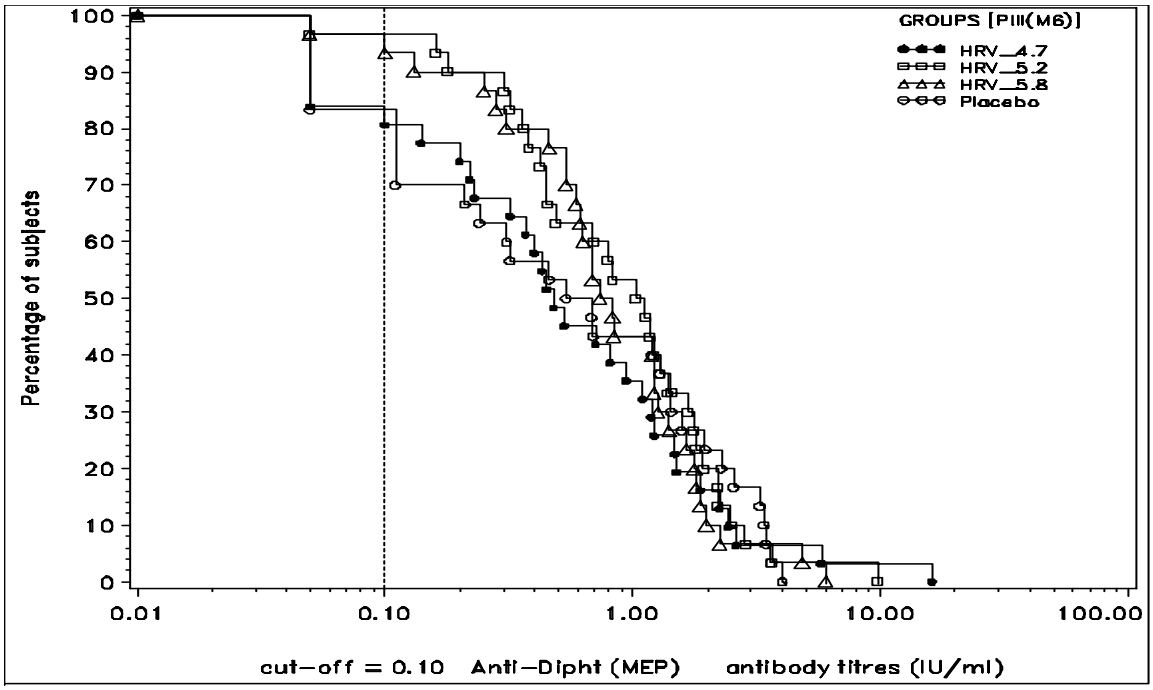
Supplement 179: Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations two months after Dose 2 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



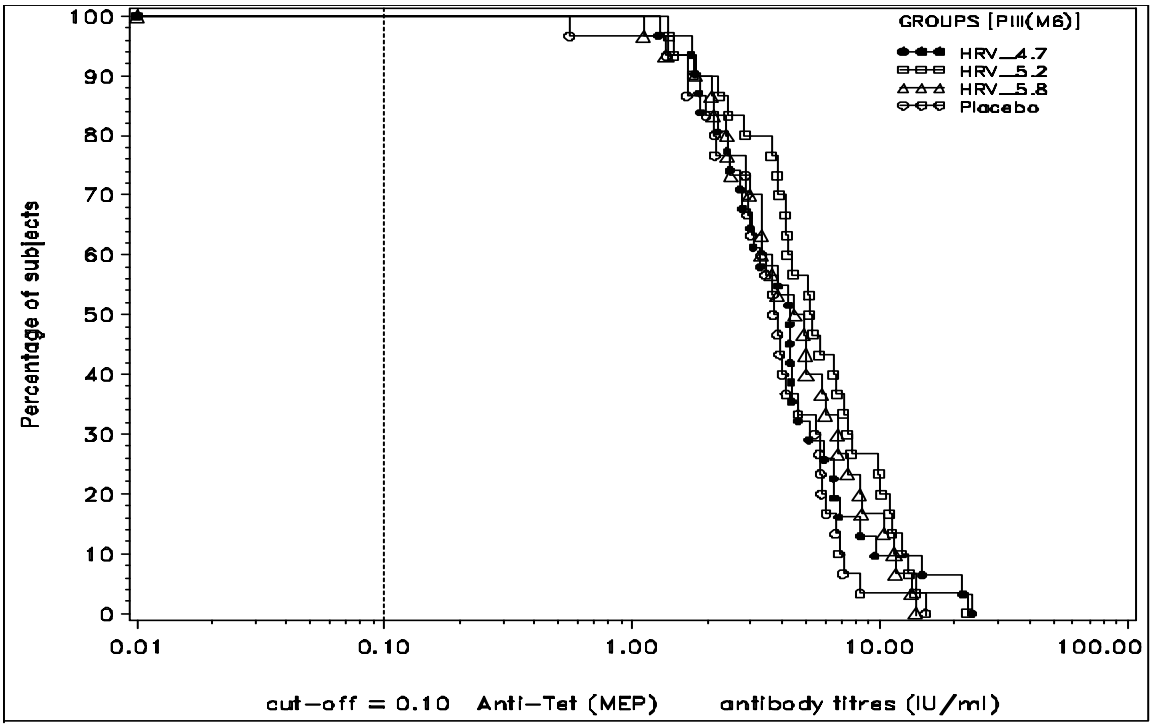
Supplement 180: Reverse cumulative curves for anti-rotavirus IgA antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



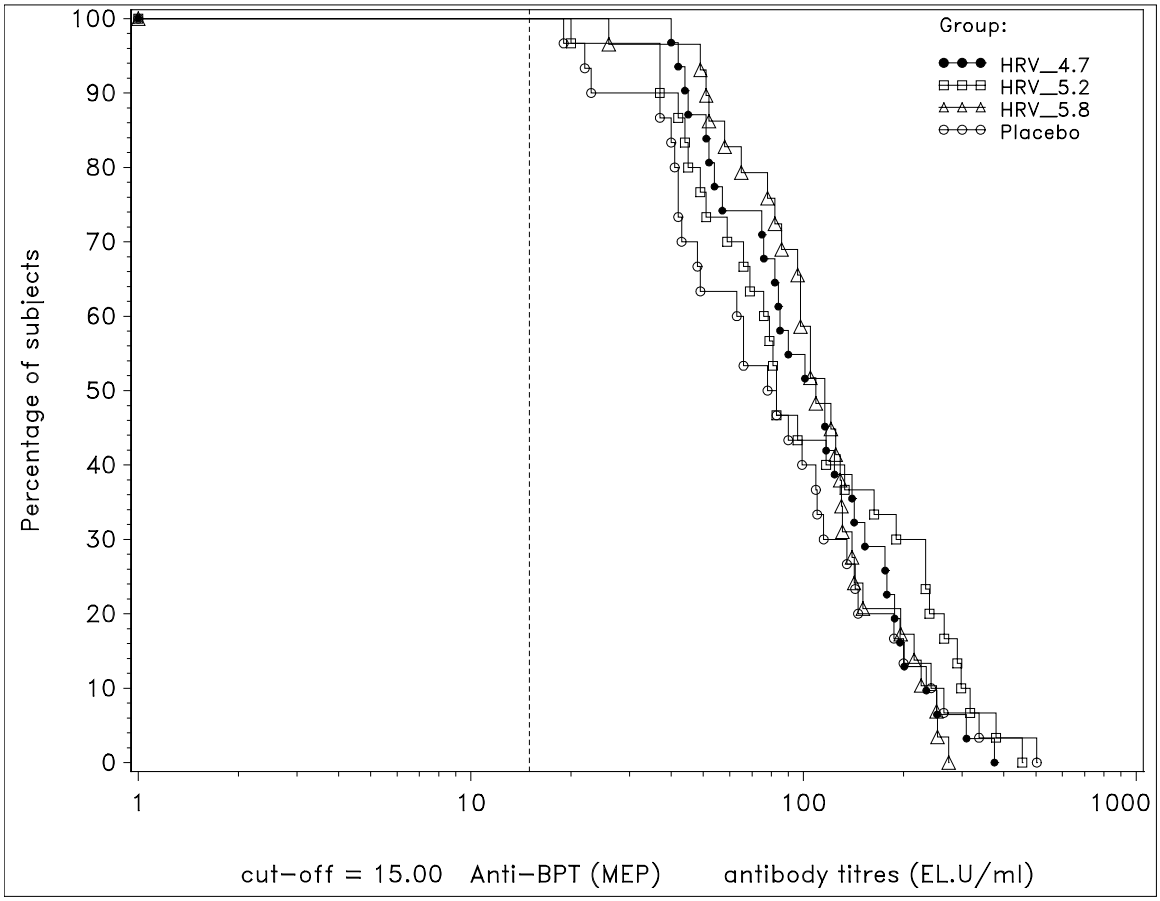
Supplement 181: Reverse cumulative curves for anti-diphtheria antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



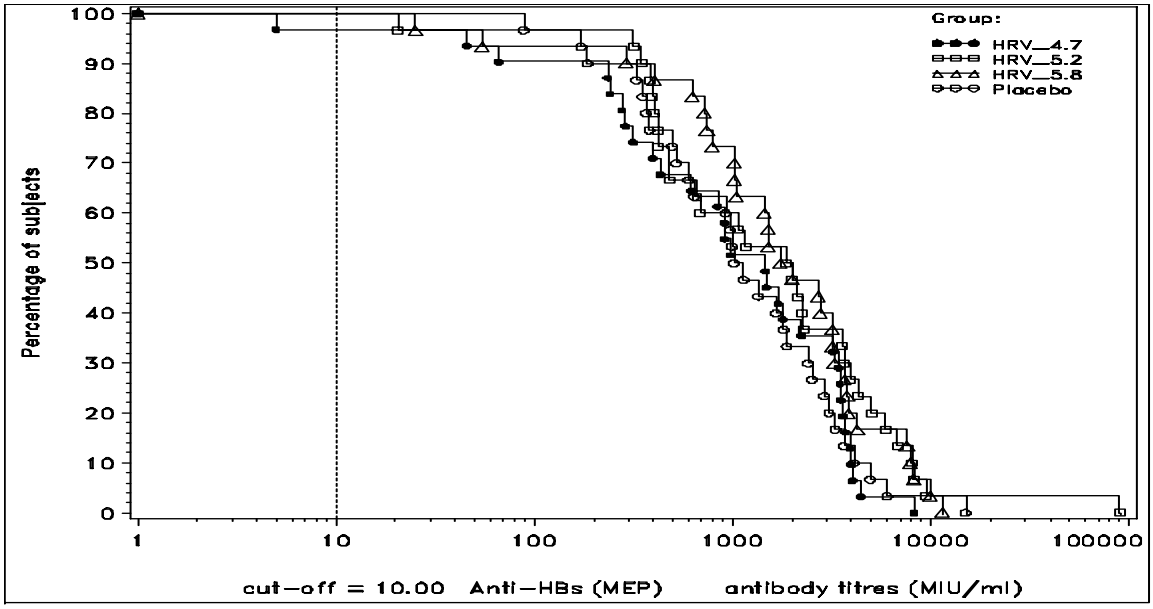
Supplement 182: Reverse cumulative curves for anti-tetanus antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



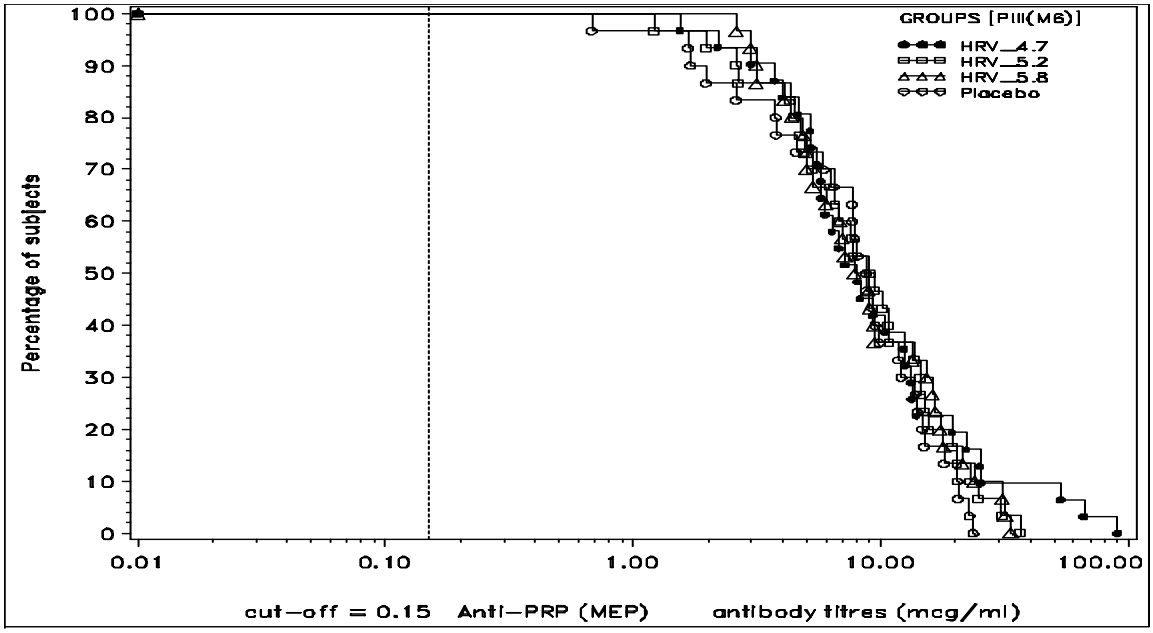
Supplement 183: Reverse cumulative curves for anti-BPT antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



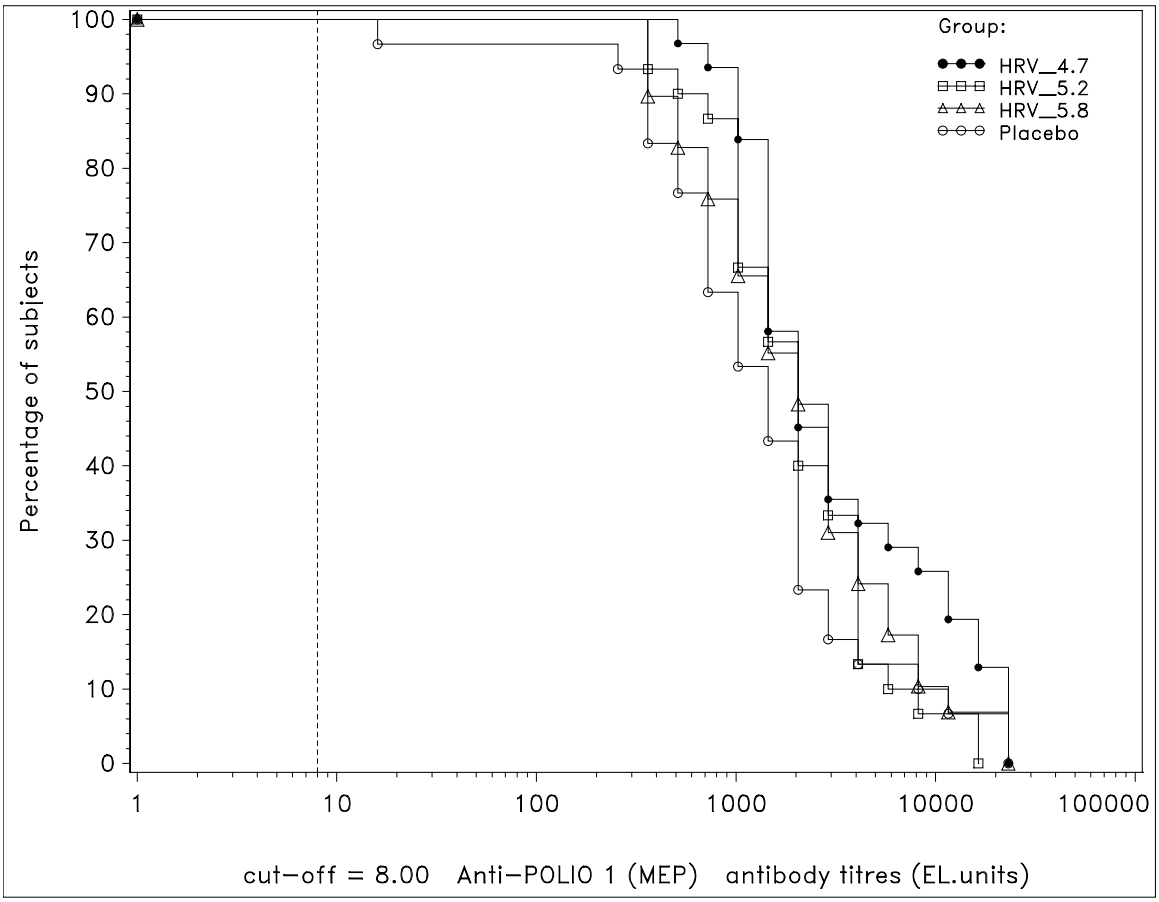
Supplement 184: Reverse cumulative curves for anti-HBs antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



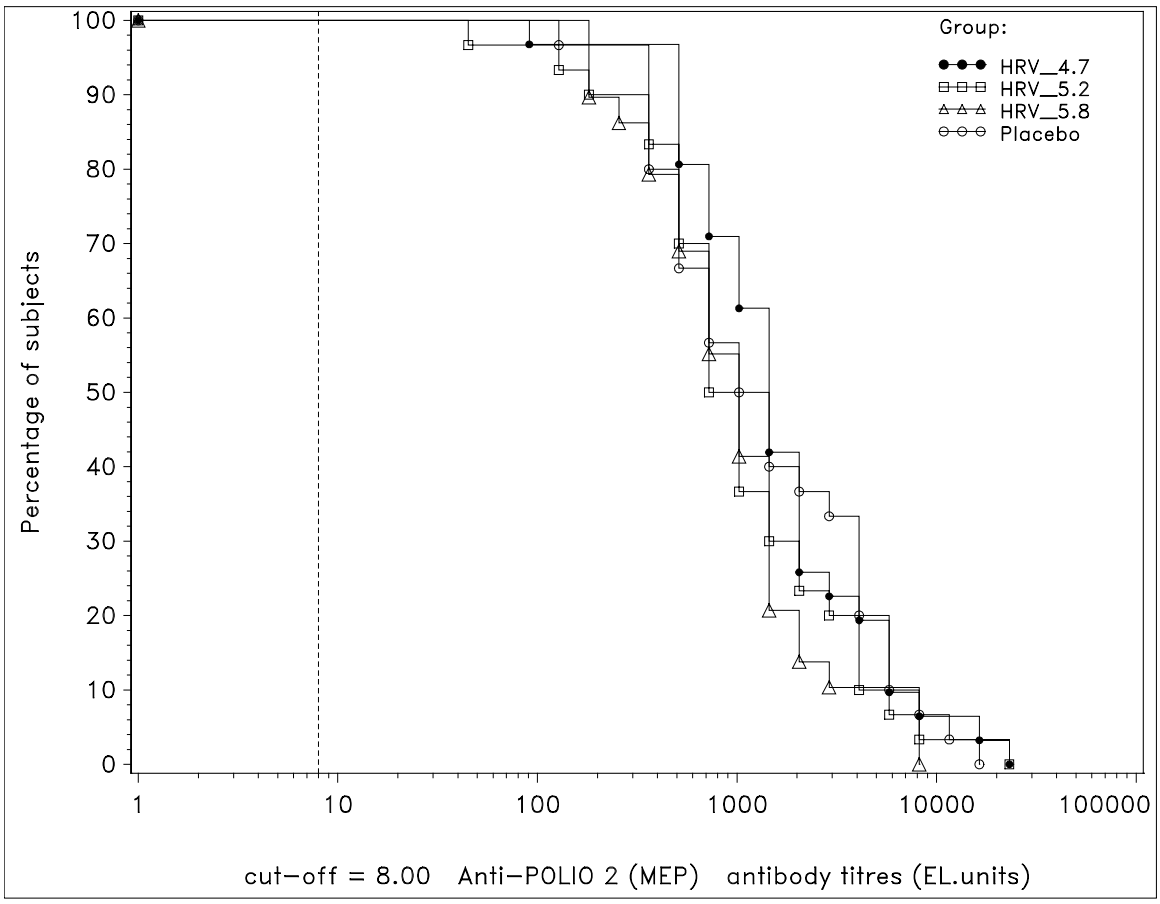
Supplement 185: Reverse cumulative curves for anti-PRP antibody concentrations two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



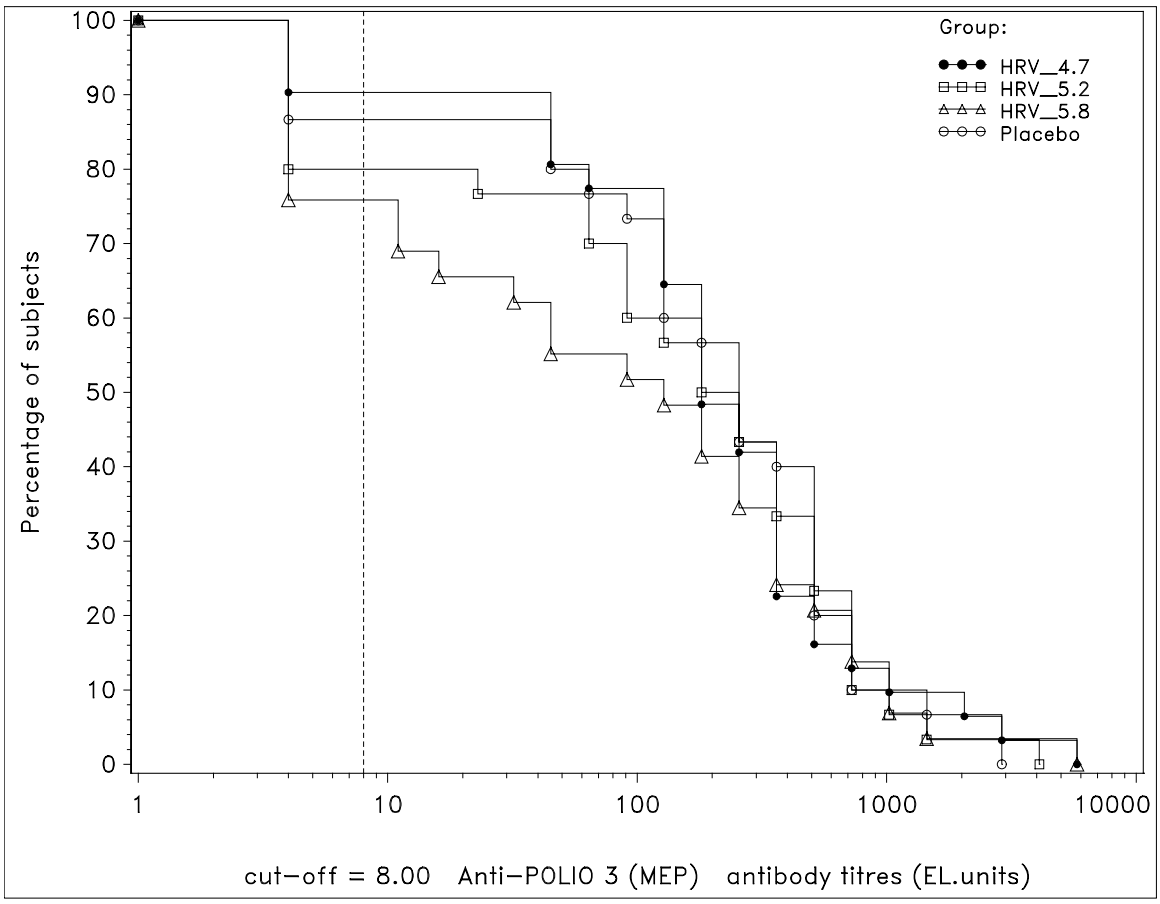
Supplement 186: Reverse cumulative curves for anti-poliovirus type 1 antibody titers two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



Supplement 187: Reverse cumulative curves for anti-poliovirus type 2 antibody titers two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



Supplement 188: Reverse cumulative curves for anti-poliovirus type 3 antibody titers two months after Dose 3 of HRV vaccine or placebo (total vaccinated cohort receiving three doses of study vaccine)



GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

CONFIDENTIAL

Study Reporting and Analysis Plan for clinical trial 444563/006

Title: A phase IIb, double-blind, randomised, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of SmithKline Beecham Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with human rotavirus, when administered concurrently with DTPw-HBV, Hib vaccine.

This Study RAP is to consider with respect to the Rotavirus Project RAP

CPMS Study No.	444563/006 (Rota-006)
Date	June 12 2003
Version	Final
Authors	[redacted] Biostatistician

The content of this document is CONFIDENTIAL and the PROPRIETARY PROPERTY of GlaxoSmithKline Biologicals.

Copying, disclosure or use of this documentation or any part thereof is prohibited without the written consent of GlaxoSmithKline Biologicals

GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

CONFIDENTIAL

Approved by:		
Clinical Project Director		
	[redacted]	dd-mm-yyyy
Clinical Development Manager		
	[redacted]	dd-mm-yyyy
Manager Biostatistics (Pediatric)		
	[redacted]	dd-mm-yyyy

Table of contents

1 INTRODUCTION 5

2 STUDY OBJECTIVES, ENDPOINTS AND ANALYSIS VARIABLES 5

2.1 OBJECTIVES 5

2.1.1 Primary Objectives 5

2.1.2 Secondary Objectives 5

2.2 ENDPOINTS 8

2.2.1 Primary Endpoint 8

2.2.2 Secondary Endpoints 8

2.3 ANALYSIS VARIABLES 11

3 STUDY DESIGN OVERVIEW 11

4 STUDY COHORTS/DATASETS TO BE EVALUATED 15

4.1 TOTAL VACCINATED COHORT 15

4.2 ACCORDING-TO-PROTOCOL (ATP) SAFETY COHORT (ONLY FOR THE SUBSET OF SUBJECTS RECEIVING 2 DOSES OF HRV VACCINE OR PLACEBO) 16

4.3 ATP IMMUNOGENICITY COHORT (ONLY FOR THE SUBSET OF SUBJECTS RECEIVING 2 DOSES OF HRV VACCINE OR PLACEBO) 16

4.4 ATP EFFICACY COHORT (ONLY FOR THE SUBSET OF SUBJECTS RECEIVING 2 DOSES OF HRV VACCINE OR PLACEBO) 16

4.5 ANALYSIS COHORTS 16

5 ESTIMATED SAMPLE SIZE 17

6 CHANGES FROM THE PROTOCOL 19

7 INTERIM ANALYSIS 20

8 FINAL ANALYSIS 21

8.1 STUDY COHORTS AND DEMOGRAPHY ANALYSIS 21

8.2 EFFICACY ANALYSIS 26

8.2.1 For the subset of subjects receiving 2 doses of HRV vaccine or placebo 26

8.2.2 For the subset of subjects receiving 3 doses of HRV vaccine or placebo (Total vaccinated cohort only) 29

8.3 REACTOGENICITY / SAFETY ANALYSIS 30

8.3.1 For all subjects, restricted to doses 1 and 2 of HRV/placebo 30

8.3.2 For the subset of subjects receiving 3 doses of HRV/placebo (Total vaccinated cohort only) *31*
8.4 IMMUNOGENICITY ANALYSIS 32
8.4.1 For the subset of subjects receiving 2 doses of HRV/placebo *32*
8.4.2 For the subset of subjects receiving 3 doses of HRV/placebo (Total vaccinated cohort only) *38*
8.5 LIST OF TABLES AND FIGURES 40

9 ANNEX ANALYSIS 49

9.1 STUDY COHORTS AND DEMOGRAPHY ANALYSIS 49
9.2 EFFICACY ANALYSIS 51
9.2.1 Subset of subjects receiving 2 doses of HRV vaccine or placebo *51*
9.2.2 Subset of subjects receiving 3 doses of HRV vaccine or placebo (Total vaccinated cohort only) *51*
9.3 REACTOGENICITY / SAFETY ANALYSIS 53
9.4 LIST OF TABLES AND FIGURES 54

Glossary of terms

- ***Diarrhea***: Three or more looser than normal stools within a day.
- ***First year of efficacy follow-up period*****:** Each subject will be followed for the efficacy analysis starting from two weeks post dose 2 until the age of approximately one year.
- ***Gastroenteritis***: Diarrhea.
- ***Mixed rotavirus gastroenteritis:*** Gastroenteritis associated with rotavirus and at least one other pathogen :

  an episode of rotavirus gastroenteritis for which at least one other pathogen is identified in stool sample(s) collected from the start of the gastroenteritis episode to the minimum of the following 2 timepoints either 7 days after the end of the gastroenteritis episode or the day before the next gastroenteritis episode, if subject had several episodes of gastroenteritis.

- ***Pure rotavirus gastroenteritis:*** Rotavirus gastroenteritis with no other identified concurrent pathogen infection
- ***Rotavirus gastroenteritis:*** All rotavirus gastroenterites (pure and mixed rotavirus gastroenteritis).
- ***Rotavirus gastroenteritis caused by the circulating wild-type rotavirus strains:***

  For the subset of subjects who receive two doses of HRV or placebo:

  - From Visits 1 to 3 : all gastroenterites episodes in which rotavirus other than vaccine strain is identified in a stool sample collected during the episode
  - From Visit 3 onwards : all gastroenterites episodes in which rotavirus is identified in a stool sample collected during the episode

  For the subset of subjects who receive three doses of HRV or placebo:

  - From Visits 1 to 4 : all gastroenterites episodes in which rotavirus other than vaccine strain is identified in a stool sample collected during the episode

- From Visit 4 onwards : all gastroenterites episodes in which rotavirus is identified in a stool sample collected during the episode

- ***Rotavirus gastroenteritis for efficacy analysis:*** An episode of gastroenteritis (diarrhea) occurring at least two weeks after dose 2 in which wild-type rotavirus strains is identified in a stool sample collected during the episode of gastroenteritis.

  Stool samples collected from the start of the gastroenteritis episode to the minimum of the following 2 timepoints either 7 days after the end of the gastroenteritis episode or the day before the next gastroenteritis episode, if subject had several episodes of gastroenteritis will be considered.

- ***Second year of efficacy follow-up period*****:** Approximately 1000 subject will be followed for a second efficacy analysis either until the age of two years (for subjects from Brazil and Venezuela) or until the end of the 2003 rotavirus season (for subjects from Mexico).

- **Separate episodes of gastroenteritis:** Two occurrences of gastroenteritis with 5 or more symptom-free days between the episodes.

- ***Severe rotavirus gastroenteritis:*** An episode of rotavirus gastroenteritis with score ≥ 11 on a 20 point scoring system (Ruuska, Vesikari).

- ***Vomiting:*** One or more episodes of forceful emptying of partially digested stomach contents ≥ 1 hour after feeding within a day.

1 Introduction

This Study Report and Analysis Plan (StRAP) briefly describes the context of the clinical study 444563 / 006 (Rota-006), in terms of objectives, endpoints and analysis variables (section 2), in terms of study design and procedures (section 3) and in terms of sample size (section 5), as stated in the protocol. The data included in the analyses are described in section 4.

The analyses of demography, reactogenicity, safety, immunogenicity and efficacy (sections 6, 7, 8 and 9) are performed according to the 444563 (Rotavirus) Project Reporting and Analysis Plan (PjRAP).

2 Study objectives, endpoints and analysis variables

2.1 Objectives

2.1.1 Primary Objectives

For the subset of subjects who receive two doses of HRV or placebo (N=2155).

- For a range of viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine, to demonstrate the efficacy of two doses of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations (except OPV) in preventing any rotavirus gastroenteritis* during the period starting from 2 weeks after dose 2 until the end of the first efficacy follow-up period.

* Rotavirus gastroenteritis for efficacy analysis is defined as an episode of gastroenteritis (diarrhea), occurring at least two weeks after dose 2 in which rotavirus other than vaccine strain is identified in a stool sample collected within 7 days after the onset of gastroenteritis symptoms.

2.1.2 Secondary Objectives

Efficacy

First year follow-up

For the subset of subjects who receive two doses of HRV or placebo (N=2155):

- For a range of viral concentrations ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine, to assess if two doses of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations (except OPV) can:
  - Prevent severe rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
  - Prevent rotavirus gastroenteritis due to virus types heterologous to vaccine strain from two weeks after dose 2 until the end of the first efficacy follow-up period.
  - Prevent any and severe pure rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
  - Prevent mixed rotavirus gastroenteritis (gastroenteritis associated with rotavirus and at least one other pathogen) during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
  - Prevent hospitalization for rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.

For the subset of subjects who receive three doses of HRV or placebo (N=121):

- To explore the rates of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the first efficacy follow-up period.

Second year follow-up (for a subset of about 1000 subjects) and combined efficacy follow-up periods

- To evaluate the efficacy of the HRV vaccine during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period,
- To evaluate the efficacy of the HRV vaccine during the period starting from 2 weeks after the last HRV/placebo dose until the end of the second efficacy follow-up period.

The endpoints evaluated for this second year analysis and for combined efficacy analysis (severity and nature of disease, study groups and subsets) will be similar to those evaluated during the first year of follow-up.

Immunogenicity

For the subset of subjects who receive two doses of HRV or placebo (N=2155):

- To assess vaccine take, in subjects uninfected with rotavirus before vaccination, two months after each study vaccine dose in a subset of 800 subjects. Take is defined as the appearance of serum IgA to rotavirus in post-immunization sera at a titer ≥ 20 U/ml and/or vaccine virus shedding in any stool sample collected from Visit 1 to Visit 3.
- To assess persistence of serum IgA to rotavirus at the end of the first efficacy follow-up period.
- To explore in a subset of 800 subjects the effect of GSK Biologicals' rotavirus vaccine on the immune response to concurrently administered routine vaccinations.
- To explore the effect of unrestricted feeding on the immunogenicity of the vaccine.
- To assess viral shedding in the vaccine groups in a subset (N=400).

For the subset of subjects who receive three doses of HRV or placebo (N=121):

- To assess serum IgA to rotavirus, two months after dose 2 and dose 3 of study vaccine or placebo.
- To assess viral shedding in the vaccine groups after the third HRV vaccine dose.
- To explore the effect of GSK Biologicals' rotavirus vaccine on the immune response to concurrently administered routine vaccinations two months after the third dose of routine vaccines.

Safety/Reactogenicity

- To assess the safety and reactogenicity of two doses of GSK Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations (except OPV) compared with placebo (N=2276).
- To assess the safety and reactogenicity of the third dose of GSK Biologicals' HRV vaccine at each viral concentration ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) given concomitantly with routine vaccinations (except OPV) compared with placebo in a subset of subjects (N=121).

Refer to Glossary of Terms for definition of term used.

2.2 Endpoints

2.2.1 Primary Endpoint

For the subset of subjects who receive two doses of HRV or placebo (N=2155) :

- Occurrence of any rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the first efficacy follow-up period.

2.2.2 Secondary Endpoints

Efficacy endpoints

For the subset of subjects who receive two doses of HRV or placebo (N=2155).

- Occurrence of severe rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
- Occurrence of rotavirus gastroenteritis due to virus types heterologous to vaccine strain during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
- Occurrence of any and severe pure rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
- Occurrence of rotavirus gastroenteritis in which there is at least one other pathogen during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.
- Occurrence of hospitalization for rotavirus gastroenteritis during the period starting from two weeks after dose 2 until the end of the first efficacy follow-up period.

For the subset of subjects who receive three doses of HRV or placebo (N=121):

- Occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the first efficacy follow-up period.

For the subset of subjects who participate in a second year of efficacy follow-up (N~1000):

For the subset of subjects who receive two doses of HRV or placebo :

- occurrence of any and severe rotavirus gastroenteritis during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.
- occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the second efficacy follow-up period.

For the subset of subjects who receive three doses of HRV or placebo:

- occurrence of any and severe rotavirus gastroenteritis during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period.
- occurrence of any and severe rotavirus gastroenteritis during the period starting from 2 weeks after dose 3 until the end of the second efficacy follow-up period.

Immunogenicity endpoints

For the subset of subjects who receive two doses of HRV or placebo (N=2155).

- Serum rotavirus IgA antibody titers at Visit 1 and the end of the first efficacy follow-up period and at Visits 2 and 3 in a subset (N=800).
- Proportion of subjects with vaccine take at visits 2 and 3 in a subset (N=800).
- Vaccine take and GMTs of rotavirus IgA ELISA will be calculated in a subset for breast fed infants compared with formula fed infants for the following 3 categories: 1) whether the infant received no food 1 hour prior to and 30 minutes after dose 1 or dose 2 (as reported by the mother); 2) whether the infant received food 1 hour prior to dose 1 or dose 2 (as reported by the mother); and 3) whether the infant received food within 30 minutes after dose 1 or dose 2.
- Viral shedding in the vaccine groups in a subset (N = 400).

Two months after dose 2 (at Visit 3) and after dose 3 at year 1 (Visit 4) in a subset (800 subjects) :

- GMTs for anti-PRP, anti-diphtheria and anti-tetanus toxoids, anti-BPT, anti-polio type 1, 2 and 3 and anti-HBs.

- Seroprotection status:
  - ◊ anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
  - ◊ anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-HBs antibody concentrations ≥ 10.0 mcg/ml
  - ◊ anti-polio type 1 antibody titers ≥ 8
  - ◊ anti-polio type 2 antibody titers ≥ 8
  - ◊ anti-polio type 3 antibody titers ≥ 8
- Seropositivity status:
  - ◊ anti-BPT antibody concentrations ≥ 15 EL.U/ml

For the subset of subjects who receive three doses of HRV or placebo (N=121):

- Serum rotavirus IgA antibody titers at visit 1, 3 and 4.
- GMTs for anti-PRP, anti-diphtheria and anti-tetanus toxoids, anti-BPT, anti-polio types 1, 2 and 3 and anti-HBs, two months after dose 3.
- Seroprotection status two months after dose 3:
  - ◊ anti-PRP antibody concentrations ≥ 0.15 and ≥ 1.0 mcg/ml
  - ◊ anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/ml
  - ◊ anti-HBs antibody concentrations ≥ 10.0 mcg/ml
  - ◊ anti-polio type 1 antibody titers ≥ 8
  - ◊ anti-polio type 2 antibody titers ≥ 8
  - ◊ anti-polio type 3 antibody titers ≥ 8
- Seropositivity status two months after dose 3:
  - ◊ anti-BPT antibody concentrations ≥ 15 EL.U/ml
- Viral shedding in the vaccine groups on the day of and on day 7 after dose 3.

Safety endpoints

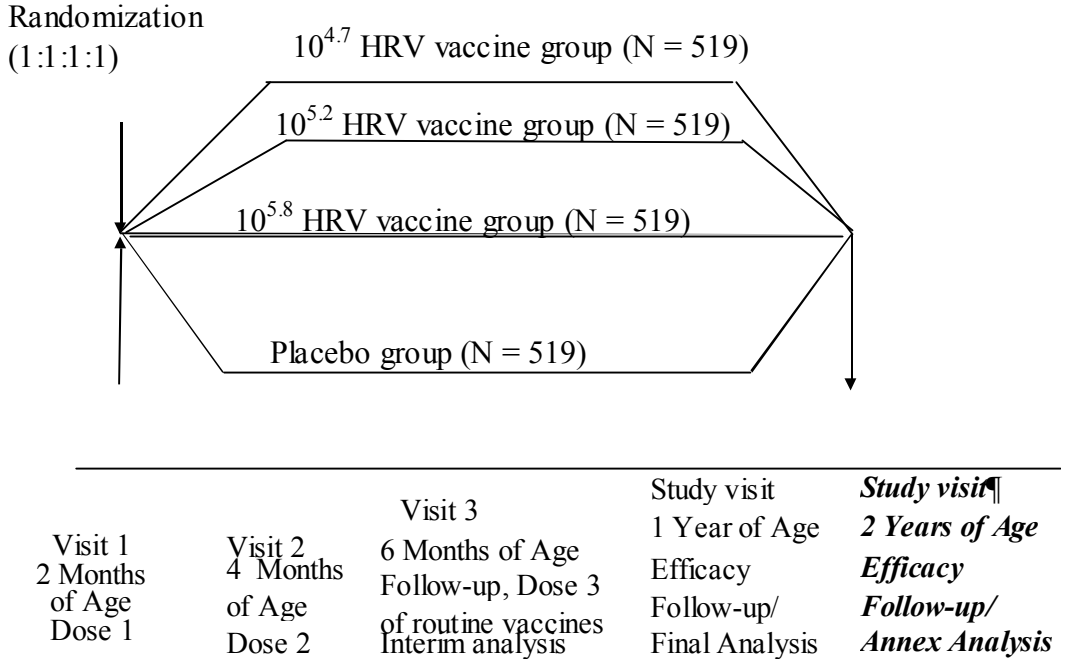
- For each type of solicited symptoms, occurrence of the symptom within the 15-day solicited follow-up period after any dose of study vaccine (in a subset after dose 3 as well).
- Occurrence of unsolicited symptoms within 42 days after dose 1, dose 2 (in all subjects) and dose 3 (in a subset), according to WHO classification.
- Occurrence of serious adverse events throughout the entire study period.

2.3 Analysis variables

The demography, reactogenicity, safety, immunogenicity and efficacy variables are those described in section 3 of the 444563 (Rotavirus) PjRAP.

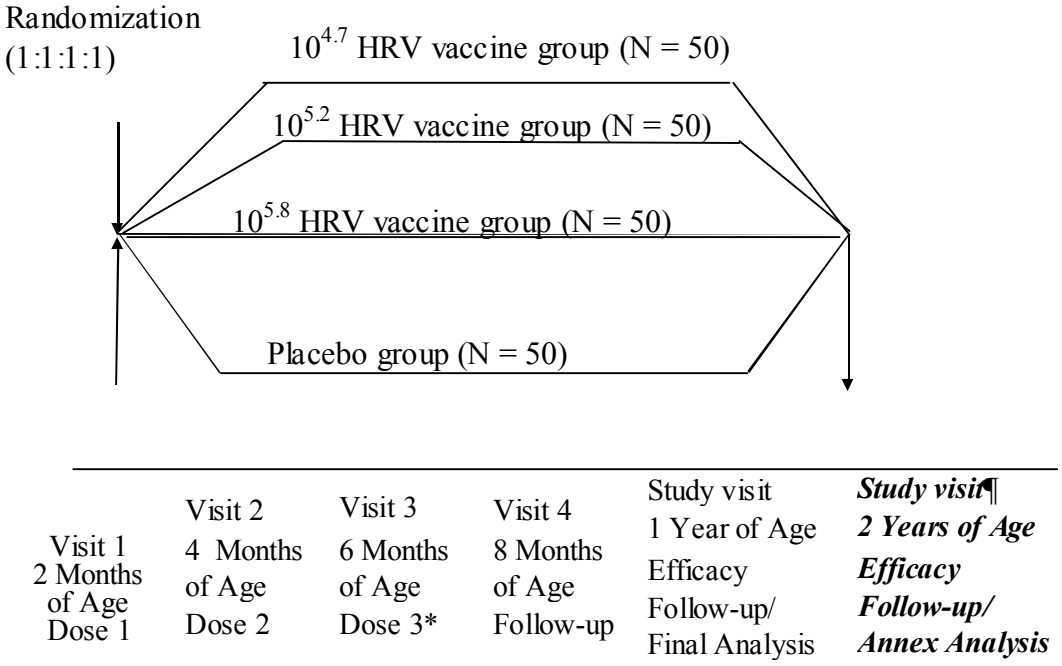
3 Study design overview

For the subset of subjects receiving two doses of HRV or placebo:



¶*In a subset of subjects*

For the subset of subjects receiving three doses of HRV or placebo:



*HRV vaccine/placebo and routine vaccines
¶*In a subset of subjects*

- Experimental design: Double-blind, randomized, placebo-controlled, with four parallel groups.
- All subjects will be followed for efficacy until one year of age and a subset, about 1000 subjects, will be followed for a second efficacy follow-up period (until age 18 - 24 months).
- Study will be conducted independently in Brazil, Mexico and Venezuela.
- For the subjects who participate only in the first year of efficacy follow-up (until age 12 months), the intended duration of the study, per subject, will be approximately 10 months for subjects.
  For the subset of subjects who participate in a second year of efficacy follow-up (until age 18 - 24 months), the intended duration of the study, per subject, will be approximately 16 - 22 months.

Study Procedures

- Hepatitis B, BCG and OPV vaccination at birth is allowed according to local Expanded Program of Immunization [should be documented in the electronic Case Report Form (eCRF)].
- Routine vaccinations (DTPw-HB+Hib vaccine) should be administered concomitantly with the study vaccines at 2 and 4 months of age; thereafter, DTPw-HB+Hib vaccine will be given at 6 months of age. Oral polio vaccination will be given at the discretion of the investigator, but should not be administered during the period starting 2 weeks before each dose of study vaccine and ending 2 weeks after. Routine vaccinations, including OPV, must be documented in the eCRF.
- There will be no restrictions on feeding the infants before or after study vaccines' administration.
- A subset of subjects (N =121) enrolled in Brazil will receive a third dose of the HRV vaccine or placebo.
- Active follow-up for safety and gastroenteritis via weekly visits to a subject by study personnel (Health Worker) starting 1 week after dose 1 and ending at the study visit at the end of the second efficacy follow-up period. For the subjects who participate only in the first year of efficacy follow-up, active follow-up for safety and gastroenteritis via weekly visits to a subject by study personnel (Health Worker) will end at the study visit at the end of the first efficacy follow-up period.
- 15-day follow-up period (day 0 to day 14) on solicited symptoms (fever, fussiness / irritability, diarrhea, vomiting, loss of appetite and cough/runny nose) after any dose of study vaccine using diary cards (in a subset of 121 subjects after dose 3).
- Blood samples will be drawn from all subjects at study Visit 1, from all subjects receiving two doses of study vaccine or placebo at the end of the first efficacy follow-up period and in a subset (N = 800) at Visits 2 and 3. Blood samples will be drawn from the subset receiving three doses of study vaccine or placebo (N =121) at Visit 3 (two months after dose 2) and Visit 4 (two months after dose 3).
- Recording of unsolicited symptoms within 42 days after dose 1, dose 2 (in all subjects), and dose 3 (in a subset of 121 subjects) of the study vaccines.
- Recording of serious adverse events throughout the study period.
- Information on feeding on the day of each study vaccine administration will be recorded for all subjects. The parent/guardian will be questioned whether the child is fed with breast milk or infant formula and whether the child was

fed within 60 minutes before vaccination and/or within 30 minutes after vaccination.

- Stool samples will be collected from a subset of 400 subjects from the subset receiving two doses of study vaccine/ placebo on the day of administration of dose 1 and dose 2 and on day 7 following each dose of study vaccine. Stool samples will be collected from the subset receiving three doses of study vaccine/placebo (N=121) on the day of administration of dose 3 and on day 7 following dose 3 of study vaccine.
- For each suspected gastroenteritis episode occurring from day of dose 1 until study end, a stool sample will be collected as soon as possible after the onset of gastroenteritis and will be brought as soon as possible to the study site. A second stool specimen will be collected if the first stool sample was not sufficient.
- All stool samples collected at pre-determined timepoints and in case of gastroenteritis episodes will be tested by ELISA at Laboratory of Dr. [redacted] Cincinnati, US to determine the presence of rotavirus. All positive samples collected in case of gastroenteritis episodes will be tested by PCR to determine G type. If any G1 rotavirus is detected in the stool specimens between Visit 1 and Visit 3 (Visit 4 for the subset receiving three doses of study vaccine or placebo), vaccine virus will be differentiated from the wild type serotype by sequence analysis or an equivalent approach.

  In addition, during the first year of efficacy follow-up, if rotavirus is detected (by rapid rotavirus detection kit used locally) in the stool sample, part of the stool samples should be analysed locally for culture of enteric pathogens such as Salmonella, Shigella, and Campylobacter to determine the presence/absence of mixed infections. ETEC and EPEC will be determined at a central laboratory.

  An episode of gastroenteritis will be classified positive for rotavirus if the stool samples collected during the episode are positive as tested by Rota Ag ELISA at Laboratory of Dr. [redacted]
- As part of a site-specific sub-study in Venezuela, stool samples, up to a maximum of 10 over the study period, will be collected from a subset of 200 subjects enrolled in Venezuela. Also, two additional stool samples will be collected from this subset during each gastroenteritis episode occurring during the study period. Results of these analyses will not be part of the clinical study report.
- Data collection will be by remote data entry.

Selection of subsets

Subset	N	Selection
Subjects planned to receive 2 doses of HRV or placebo (subset A)	2155	subjects for whom Visit 3 were done at the time of the approval of the amendment 3 of the protocol (May 3, 2002).
➢ Subjects bled at Visits 2 and 3 (from subset A)	800	The first subjects enrolled in each country, amounting to at least 200 subjects in each of the 3 participating countries.
➢ Subjects for whom stool samples were collected at pre-determined time points (from subset A)	400	The first subjects enrolled in each country, amounting to at least 100 subjects in each of the 3 participating countries.
Subjects planned to receive 3 doses of HRV or placebo	121	in Brazil, subjects for whom Visit 3 were not yet done at the time of the approval of the amendment 3 of the protocol (May 3, 2002).
Subjects followed for a second efficacy follow-up period	1000	All subjects who have not completed the follow-up visit at 1 year of age as of October 31, 2002.

4 Study cohorts/Datasets to be evaluated

The target population consists of healthy male and female infants between 6 and 12 weeks of age. Inclusion and exclusion criteria are as defined in the protocol (section 4.2 and 4.3).

Subjects who received OPV during the period starting 2 weeks before any study vaccine and ending 2 weeks after will be eliminated from the ATP cohorts.

4.1 Total vaccinated cohort

As defined in section 2.1.1 of the PjRAP.

For the subset of subjects receiving 3 doses of HRV vaccine or placebo :

an efficacy analysis based on the total vaccinated cohort includes all vaccinated subjects for whom efficacy follow-up data is available. Efficacy follow-up is derived from any contact

- beyond 2 weeks after the third dose of HRV vaccine or placebo for the first efficacy follow-up period,
- beyond the end of the first efficacy follow-up period for the second efficacy follow-up period,
- beyond 2 weeks after the third dose of HRV vaccine or placebo for combined efficacy follow-up periods.

4.2 According-To-Protocol (ATP) Safety Cohort (only for the subset of subjects receiving 2 doses of HRV vaccine or placebo)

As defined in section 2.1.2 of the PjRAP.

4.3 ATP Immunogenicity Cohort (only for the subset of subjects receiving 2 doses of HRV vaccine or placebo)

As defined in section 2.1.3 of the PjRAP and

- for whom results (for rotavirus IgA antibodies or for stool) are available at pre-vaccination timepoint and at least one post-vaccination timepoints up to Visit 3.
- who have no rotavirus other than vaccine strain in stool samples collected from dose 1 till visit 3 (elimination code:2060 if condition is not fulfilled).

4.4 ATP Efficacy Cohort (only for the subset of subjects receiving 2 doses of HRV vaccine or placebo)

As defined in section 2.1.4 of the PjRAP.

4.5 Analysis cohorts

The total vaccinated cohort is used for the primary analysis of safety.
The analysis on the ATP cohort for safety is only performed if more than 5% of the vaccinated subjects are excluded from the ATP safety cohort.

The ATP immunogenicity cohort is used for the primary analysis of immunogenicity. An analysis of immunogenicity based on the total vaccinated cohort is only performed if more than 5% of the vaccinated subjects with available results at post-vaccination timepoints are excluded from the ATP immunogenicity cohort. In such a case, the total vaccinated cohort analyses evaluate whether exclusion from the ATP cohort have biased the results.

The ATP efficacy cohort is used for the primary analysis of efficacy.
An analysis of efficacy based on the total vaccinated cohort is also performed.

The analyses of safety, immunogenicity and efficacy for the subset of subjects who received 3 doses of HRV or placebo will be performed on the total vaccinated cohort.

5 Estimated sample size

The primary objective is to demonstrate that, for a range of viral concentration ($10^{4.7}$ ffu, $10^{5.2}$ ffu and $10^{5.8}$ ffu) of GSK Biologicals' HRV vaccine, two doses of GSK Biologicals' HRV vaccine given concomitantly with routine vaccinations (except OPV) can prevent rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the efficacy follow-up period following vaccination.

The analysis will consist in looking at the pooled vaccine groups versus placebo and each vaccine group versus placebo.

In order to control the risk of falsely concluding below 5%, the primary objective will be addressed using a hierarchical testing. Pooled vaccine groups will be first tested and, only if efficacy has been demonstrated, will the vaccine with a viral concentration of $10^{5.8}$ ffu be tested. Likewise, only if efficacy of vaccine with a viral concentration of $10^{5.8}$ ffu has been demonstrated, will the vaccine with a viral concentration of $10^{5.2}$ ffu be tested. Likewise, only if efficacy of vaccine with a viral concentration of $10^{5.2}$ ffu has been demonstrated, will the vaccine with a viral concentration of $10^{4.7}$ ffu be tested. Efficacy will be established if the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the efficacy follow-up period following vaccination in the HRV group is statistically significantly lower than in the placebo group (two-sided Fisher Exact test : $p < 0.05$).

The target sample size was planned at 2640 enrolled subjects to reach 2360 subjects in the ATP cohort of efficacy (590 in each group). However, the target

sample size has been reduced because of difficulty in enrolling eligible subjects for participation in the study. In addition, a subset of approximately 121 subjects will receive 3 doses of HRV vaccine or placebo. Target enrollment for subjects who will receive only 2 doses of HRV vaccine or placebo is estimated to be 2076 eligible subjects leaving 460 evaluable subjects per group for the analysis of the primary objective.

Table 1 indicates the level of accuracy that can be expected for the evaluation of efficacy for a vaccine group to any rotavirus gastroenteritis (primary objective) and to severe rotavirus gastroenteritis (secondary objective) with this sample size. Power is higher for the evaluation of efficacy on pooled vaccine groups.

Table 1: Power to get an exact 95% CI for the vaccine efficacy above a specific cut-off (N=460 subjects by group, power based on 1.000 simulations using Proc StatXact)

% of subjects reporting rotavirus gastroenteritis in the placebo group from two weeks after dose 2 until the end of the efficacy follow-up period following vaccination	**% of subjects reporting rotavirus gastroenteritis in the vaccine group from two weeks after dose 2 until the end of the efficacy follow-up period following vaccination**	**Efficacy (%)**	**Cut-off**			
			0%	**10%**	**20%**	**30%**
Any Gastroenteritis						
12%*	3.6%	70%	99.7%	99.2%	97%	88.9%
12%*	4.8%	60%	96.8%	92.0%	81.8%	58.1%
12%*	6 %	50%	84.1%	71.1%	48.8%	26.7%
10%	3%	70%	98.8%	97.4%	92.4%	82.2%
10%	4%	60%	93.5%	84.8%	71.4%	51.2%
10%	5%	50%	77.4%	61.7%	41.4%	20.5%
Severe Gastroenteritis			**0%**	**10%**	**20%**	**30%**
4%*	0.8%	80%	89%	84%	76%	
4%*	1%	75%	80%	74%	63%	
4%*	1.2%	70%	72%	62%	50%	
3%	0.6%	80%	75%	68%	61%	
3%	0.75%	75%	63%	52%	44%	
3%	0.9%	70%	56%	45%	37%	

*anticipated incidence rate

With respect to the year 2 efficacy follow-up, considering an attack rate of 12% for any gastroenteritis, a 60% VE and a sample size of 200 in each vaccine group, the power to detect a statistically significant vaccine effect with the pooled

vaccine group and each vaccine group is 88% and 67% (2 sided fisher exact test, alpha=5%, no adjustment for multiplicity).

A secondary objective is to assess the immunogenicity of the concomitant routine vaccinations (diphtheria, tetanus, pertussis, PRP and HBs) and OPV in each group, two months after the second dose of the primary vaccination course and 6 months after the third dose.

Using an estimation of the seroprotection rates between 90% and 98% (for anti-diphtheria, anti-tetanus, anti-PRP, anti-HBS, anti-polio type 1, 2 and 3 antibodies) and an anti-BPT GMT of 27.3 (with a standard deviation of 0.332) (reference study: DTPw-HBV-Hib-003), and assuming that the rates / GMT are the same in the vaccine and placebo groups, a subset of 175 evaluable subjects per group will provide 80% global power that, for all vaccine groups, all the 95%CIs on the decrease in seroprotection rates with the vaccine group as compared to the placebo group are below 15% and that the 95%CIs on the fold decrease in anti-BPT GMTs for each vaccine group as compared to the placebo group is below 1.5 (power based on 1000 simulations with proc StatXact for the difference in seroprotection rates and using Nquery for the ratio of anti-BPT GMTs, one sided equivalence test, alpha=2.5%).

A total of 200 subjects by group will be bled to compensate for 12% non-evaluable subjects for the immunogenicity analysis.

6 Changes from the protocol

The total vaccinated cohort includes all subjects with at least one study vaccine administration documented. For the Total analysis of safety, this includes all vaccinated subjects with at least one vaccine administration documented and not for whom safety data are available as planned in the protocol. Doses administered without any documentation on safety data are considered as doses not followed by any symptoms.

For exploratory analyses, an increase in the incidence of specific symptoms with HRV (pooled HRV groups) as compared to placebo, will be detected using a two-sided Fisher Exact test (with an alpha of 5%) instead of a one-sided Fisher Exact test (with an alpha of 5%) to standardize the data with future studies.

According to the protocol, inference on the difference of two proportions was to be done using the exact method by Santner and Snell (ref 1). This was the only exact method available from Proc StatXact Version 3/4 (Cytel®).
However different evaluations of the Santner and Snell method indicated that this method provides overly conservative confidence interval especially when the proportions are close to 100% or 0% (ref. 2). As a consequence Cytel® does not recommend the use of the Santner and Snell method in its Proc StatXact version 5 (ref 3) anymore. Exact (ref 5) and asymptotic (ref 4) methods based on a standardized score statistic have been proposed instead. These 2 methods lead to very similar CIs for a sample size in the range of the one used in this study. However the time duration to run the exact method is considerably longer as compared to asymptotic. This is why the asymptotic method will be used for analyzing the study. While it is ensuring that the type I error is maintained, it leads to narrower CI as compared to the Santner and Snell. Therefore neither the type I error and the power are impaired by this change.

7 Interim Analysis

- An interim analysis was performed in March 2002 to provide early information for dose selection. This analysis presented a descriptive summary of immunogenicity and reactogenicity for the study vaccine as well as immunogenicity data for routine vaccines. No study report was written for the interim data and results were strictly controlled. Unblinding at the level of individual data was restricted to the statistician and the database administrator.
- An interim analysis on efficacy against any and severe rotavirus gastroenteritis, overall and by serotype was performed in August 2002 to obtain preliminary efficacy data. This interim efficacy analysis was performed when approximately 70 rotavirus gastroenteritis cases from two weeks after dose 2 were reached. This allowed to demonstrate vaccine efficacy (with LL of 95CI > 0) with 75% power based on the following conservative assumptions: vaccine efficacy (for pooled HRV vaccine groups) against any rotavirus gastroenteritis is 50%, with an attack rate of 6% in the placebo group. No study report was written for the interim efficacy data and distribution of the results was strictly controlled. Unblinding at the level of individual data was restricted to the statistician and the database administrator.
- A complementary analysis considering efficacy from dose 1 was performed in September 2002.

- An interim analysis was performed on post-dose 3 data in February 2003. This analysis presented a descriptive summary of immunogenicity for the study vaccine. No study report was written for the interim data and results were strictly controlled. Unblinding at the level of individual data was restricted to the statistician and the database administrator.
- An interim analysis on efficacy against any and severe rotavirus gastroenteritis at the end of the second efficacy follow-up period in Mexico will be performed to obtain early efficacy data. No study report will be written and distribution of the results will be strictly controlled. Unblinding at the level of individual data will be restricted to the statistician and the database administrator.

The results of interim immunogenicity post-dose 2 and post-dose 3 data, and of interim efficacy data were or may be presented at scientific conferences and, as required, to the authorities.

8 Final Analysis

The final analysis will be performed at the end of the first efficacy follow-up period, after all enrolled subjects have completed the study visit at the end of the first efficacy follow-up period. Till the end of the study (end of year 2 follow-up), only the statistician, database administrator and medical writer (for SAEs only) will have access to the individual treatment decode.

Analysis of data collected during the period starting from the end of the first efficacy follow-up period until the end of the second efficacy follow-up period will be presented in an annex report.

Sections presenting demography, immunogenicity, reactogenicity/safety and efficacy evaluation contain the summary tables and figures presented in the PjRAP.

8.1 Study cohorts and demography analysis

All the tables mentioned in section 4.1. of the PjRAP will be generated for this study, separately for the subset of subjects receiving 2 doses of HRV vaccine or placebo and for the subset of subjects receiving 3 doses of HRV vaccine or placebo.

Table 4 (for the total vaccinated cohort) will also be done by country (Brazil, Mexico, Venezuela) for the subset of subjects receiving 2 doses of HRV or placebo

In each of these tables, the following order will be used:

- HRV $10^{4.7}$
- HRV $10^{5.2}$
- HRV $10^{5.8}$
- Pooled HRV groups
- Placebo

In addition, the weight and height increase from visit 1 will be summarized by group for all Visits, as in the following tables :

Increase in height and weight from Visit 1 to Visits 2, 3 and 4, for the subset of subjects receiving 2 doses of study vaccine/placebo
(Total vaccinated cohort)

Visit	**Characteristics**	**Parameters or Categories**	**Each Group (N =XXX) Value**	**Total (N =XXX) Value**
	Increase in height (cm) from Visit 1	Mean SD Median Unknown		
	Increase in weight (kg) from Visit 1	Mean SD Median Unknown		

N= total number of subjects in the considered cohort, by group or in total (sum for all groups)
Value = value of the considered parameter
SD= standard deviation

Increase in height and weight from Visit 1 to Visits 2, 3, 4 and 5 for the subset of subjects receiving 3 doses of study vaccine/placebo
(Total vaccinated cohort)

Visit	**Characteristics**	**Parameters or Categories**	**Each Group (N =XXX) Value**	**Total (N =XXX) Value**
	Increase in height (cm) from Visit 1	Mean SD Median Unknown		
	Increase in weight (kg) from Visit 1	Mean SD Median Unknown		

N= total number of subjects in the considered cohort, by group or in total (sum for all groups)
Value = value of the considered parameter
SD= standard deviation

The following tables will also be generated, separately for the subset of subjects receiving 2 doses of HRV vaccine or placebo birth (ATP immunogenicity cohort, Total vaccinated cohort if required) and for the subset of subjects receiving 3 doses of HRV vaccine or placebo (Total vaccinated cohort*)* :

Percentage of subjects who received OPV at birth

Characteristics	***(Each group)*** **N**	**n**	**%**
OPV at birth			

Notes : N=number of subjects in the considered cohort
n/%= number/percentage of subjects with OPV given at birth

Summary of feeding criteria

Dose	***Group***	**N**	**Feeding criteria**					
			Breast milk		**Infant formula**		**Both**	
			n	**%**	**N**	**%**	**n**	**%**
(Each dose)	(Each group)							

Notes : N=number of subjects with available data
n/%= number/percentage of subjects with the specified feeding criteria

***Working table** : Percentage of subjects in each of the feeding criteria category used in the logisitc regression (only for the subset of subjects receiving 2 doses of HRV vaccine or placebo - ATP immunogenicity cohort)*

Category	**Dose**	***(Each group)*** **N** **n** **%**
Breast fed	at both doses at the first dose only at the second dose only for none of the doses	
Breast fed + formula fed	at both doses at the first dose only at the second dose only for none of the doses	
Fed within 1 hour before vaccination	at both doses at the first dose only at the second dose only for none of the doses	
Fed within 30 minutes after vaccination	at both doses at the first dose only at the second dose only for none of the doses	

Notes : N=number of subjects in the considered cohort
n/%= number/percentage of subjects in the specified category

In this study, the intervals for the age range and between visits are as follows:

- Intervals between study visits* for subjects included in the subset receiving 2 doses of study vaccine/placebo will be as follows

Interval	**Protocol intervals**	**Adapted intervals**
Age	6 – 12 weeks	Not adapted
1 (Visit 1→Visit 2)	49 - 83 days	Not adapted
2 (Visit 2→Visit 3)	49 - 83 days	Not adapted
3 (Visit 3→ First efficacy follow-up visit)	160 - 200 days	No subjects will be eliminated for not respecting the time interval between Visits 3 and first efficacy follow-up visit

*The date of the previous visit is the reference date.

- Intervals between study visits* for subjects included in the subset receiving 3 doses of study vaccine/placebo will be as follows

Interval	Protocol intervals	Adapted intervals
Age	6 – 12 weeks	No subjects will be eliminated for not respecting these time intervals
1 (Visit 1→Visit 2)	49 - 83 days	
2 (Visit 2→Visit 3)	49 - 83 days	
3 (Visit 3→Visit 4)	49 – 83 days	
4 (Visit 3→ First efficacy follow-up visit)	160 - 200 days	

*The date of the previous visit is the reference date.

8.2 Efficacy analysis

8.2.1 For the subset of subjects receiving 2 doses of HRV vaccine or placebo

All the tables mentioned in section 4.4. of the PjRAP will be generated for this study. Three country (=geographical areas in the PjRAP) are considered : Brazil, Mexico and Venezuela.

In each of these tables, the following order will be used:

- HRV $10^{4.7}$
- HRV $10^{5.2}$
- HRV $10^{5.8}$
- Pooled HRV groups
- Placebo

In addition, the following table will be generated to describe the presence of mixed infections :

Percentage of rotavirus gastroenteritis episodes with mixed infections during the first efficacy follow-up period
ATP efficacy cohort (Total vaccinated cohort)

	First efficacy follow-up period			
	(Each vaccine group)		**Placebo**	
	N=		**N=**	
Infections	**n**	**%**	**n**	**%**
Salmonella				
Shigella				
Campylobacter				
ETEC				
EPEC				
EAgEC				
EIEC				
Other				

N= number of rotavirus gastroenteritis episodes reported in each group
n/% = number/percentage of rotavirus gastroenteritis episodes with the specified mixed infection reported

To assess the efficacy of HRV against rotavirus gastroenteritis with presence/absence of mixed infections, Table 22 of the PjRAP will be generated for pure rotavirus gastroenteritis episodes and for mixed rotavirus gastroenteritis episodes.

In addition, the efficacy of HRV against hospitalization for rotavirus gastroenteritis will be computed and presented as in Table 22 of the PjRAP.

The primary objectives, addressed using a hierarchical testing procedure, is to demonstrate that :

1. The efficacy of the pooled HRV vaccine groups can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period

   If the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the first efficacy follow-up period following vaccination in the pooled HRV groups is statistically significantly lower than in the placebo group (two-sided Fisher Exact test: $p < 0.05$), one will conclude that the efficacy of the pooled HRV vaccine groups

in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period has been demonstrated.

2. HRV vaccine with a viral concentration of $10^{5.8}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period,

   If the previous primary objective has been demonstrated and if the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the first efficacy follow-up period following vaccination in the HRV group with a viral concentration of $10^{5.8}$ ffu is statistically significantly lower than in the placebo group (two-sided Fisher Exact test : $p < 0.05$), one will conclude that the efficacy of the HRV vaccine with a viral concentration of $10^{5.8}$ ffu in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period has also been demonstrated.

3. HRV vaccine with a viral concentration of $10^{5.2}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period,

   If the previous primary objectives have been demonstrated and if the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the first efficacy follow-up period following vaccination in the HRV group with a viral concentration of $10^{5.2}$ ffu is statistically significantly lower than in the placebo group (two-sided Fisher Exact test : $p < 0.05$), one will conclude that the efficacy of the HRV vaccine with a viral concentration of $10^{5.2}$ ffu in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period has also been demonstrated.

4. HRV vaccine with a viral concentration of $10^{4.7}$ ffu can prevent rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period.

   If the previous primary objectives have been demonstrated and if the percentage of subjects with rotavirus gastroenteritis during the period starting from 2 weeks after dose 2 until the end of the first efficacy follow-up period following vaccination in the HRV group with a viral concentration of $10^{4.7}$ ffu is statistically significantly lower than the placebo group (two-sided Fisher Exact test: $p < 0.05$), one will conclude that the efficacy of the HRV vaccine

with a viral concentration of $10^{4.7}$ ffu in preventing rotavirus gastroenteritis occurring from two weeks after dose 2 until the end of the first efficacy follow-up period has also been demonstrated.

To check the robustness with respect to the statistical analysis, vaccine efficacy against the primary endpoint and its 95% CI will also be estimated by the Cox proportional-hazard model including the group effect as regressor. The Kaplan Meier survival curves will be generated to analyze the time from 2 weeks after Dose 2 to the onset of RV GE. The time will be censored at the last contact in the first efficacy follow-up period.

8.2.2 For the subset of subjects receiving 3 doses of HRV vaccine or placebo (Total vaccinated cohort only)

The following Table will be generated :

*Percentage of subjects reporting any (**severe**) rotavirus gastroenteritis from 2 weeks after Dose 3 till end of the first efficacy follow-up period - Total vaccinated cohort*

Country	**Group**	**N**	**n**	**n / N** rate	95%CI
(each country)	*- each HRV group* *- pooled HRV groups* *- placebo*				
All	*- each HRV group* *- pooled HRV groups* *- placebo*				

N = number of subjects included in each group
n = number of subjects reporting at least one rotavirus gastroenteritis episode in each group
n/N= percentage of subjects reporting at least one rotavirus gastroenteritis episode in each group
95%CI= 95%confidence intervals

In addition, efficacy after the first dose will also be computed for subjects with efficacy follow-up data available after dose 1 (efficacy follow-up is dereived from any contact after the first dose of HRV vaccine or placebo).

*Percentage of subjects reporting any (**severe**) rotavirus gastroenteritis from day of Dose 1 till end of the first efficacy follow-up period - Total vaccinated cohort*

Country	**Group**	**N**	**n**	**n / N** rate	95%CI
(each country)	*- each HRV group* *- pooled HRV groups* *- placebo*				
All	*- each HRV group* *- pooled HRV groups* *- placebo*				

N = number of subjects included in each group
n = number of subjects reporting at least one rotavirus gastroenteritis episode in each group
n/N= percentage of subjects reporting at least one rotavirus gastroenteritis episode in each group
95%CI= 95%confidence intervals

8.3 Reactogenicity / Safety analysis

8.3.1 For all subjects, restricted to doses 1 and 2 of HRV/placebo

All the Tables mentioned in section 4.2. of the PjRAP will be generated for this study.

Type 'Grade 2 or 3' will be added to Table 7 and to Working Table 4 of the PjRAP.

In each of these tables, the following order will be used:

- HRV $10^{4.7}$
- HRV $10^{5.2}$
- HRV $10^{5.8}$
- Pooled HRV groups
- Placebo

Difference in the incidence of specific solicited symptoms with HRV (pooled HRV groups) as compared to placebo will be explored using a two-sided Fisher Exact test. The comparability of the 3 HRV vaccine groups will be explored using two-sided Fisher Exact Test.
Statistically significant differences (p-value <0.05) should be interpreted cautiously since, due to the number of endpoints, the differences observed in this study are likely to occur by chance alone.

Results of these statistical tests will be presented as in the following table :

Statistical comparisons between groups for the percentage of subjects reporting each solicited symptom after any doses (Total vaccinated cohort)

			P_value			
Solicited symptoms	**Type**	**Follow-up**	**HRV10$^{4.7}$ versus HRV10$^{5.2}$**	**HRV10$^{4.7}$ versus HRV10$^{5.8}$**	**HRV10$^{5.2}$ versus HRV10$^{5.8}$**	**Pooled HRV groups versus placebo**
(Each solicited symptom)	Any	Onset 15 days				
	Any	Onset 8 days				
	Related	Onset 8 days				
	Grade 2 or 3	Onset 8 days				
	Grade 3	Onset 8 days				

Onset 8 days = onset on day 0 to 7 Onset 15 days = onset on day 0 to 14
Any = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
p_value=results of comparison of percentage of subjects reporting the specified solicited symptom after any doses between groups by two-sided Fisher's exact test (significant level of α=0.05)

In addition, Tables 6, 7, 8 and Supplement 6 of the PjRAP will also be generated by country (Brazil, Mexico, Venezuela).

8.3.2 For the subset of subjects receiving 3 doses of HRV/placebo (Total vaccinated cohort only)

The following tables mentioned in section 4.2. of the PjRAP will be generated :

- Tables 5, 6, 7, 8 and 10
- Supplement 6
- Working table 4,

Type 'Grade 2 or 3' will be added to Table 7 and to Working Table 4 of the PjRAP.

In each of these tables, pooled data from the three HRV groups will also be included.

8.4 Immunogenicity analysis

The following table describes the serological tests that will be performed at each visit :

Study Group	Blood sampling timepoint			Antigen	No. subjects
	Timing	**Month**	**Visit no.**		
Each group	Pre	0	1	rotavirus only	2276
Each group	Post I	2	2	rotavirus only	800
Each group	Post II MO 4	4	3	Concomitant + OPV + rotavirus	800
				rotavirus only	121*
Each group	Post III MO 6	6	4	Concomitant + OPV + rotavirus	121*
Each group	Post II MO 10	10	End of 1st efficacy period visit	Concomitant + OPV	800
				rotavirus	2155#

* =subset of subjects who receive 3 doses of the study vaccine or placebo

= only subjects who receive 2 doses of the study vaccine or placebo

8.4.1 For the subset of subjects receiving 2 doses of HRV/placebo

All the Tables mentioned in section 4.3. of the PjRAP, except Tables 14 and 19, will be generated for this study. Tables 15, 16, 17 and 18 of the PjRAP will be generated for the stool subset (defined as subjects with at least one available result for stools collected at pre-determined timepoints after dose 1).

Tables 11 of the PjRAP will also be generated for subjects included in the stool subset.

In each of these tables, the following order will be used:

- HRV $10^{4.7}$
- HRV $10^{5.2}$
- HRV $10^{5.8}$
- Pooled HRV groups
- Placebo

The impact of feeding on the vaccine take two months after dose 2 will be explored using a logistic regression based on the following categories :

Category	**Dose**
Breast fed	at both doses at the first dose only at the second dose only for none of the doses
Breast fed + formula fed	at both doses at the first dose only at the second dose only for none of the doses
Fed within 1 hour before vaccination	at both doses at the first dose only at the second dose only for none of the doses
Fed within 30 minutes after vaccination	at both doses at the first dose only at the second dose only for none of the doses

Tables 11 and 18 of the PjRAP will also be generated according to the findings of the logistic regression.

For the concomitant vaccination and OPV, the following tables will be generated :

GMC and seropositivity/seroprotection rates for anti- (each vaccine antigen) antibody
ATP immunogenicity cohort (Total cohort, if required)

			≥cut-off				GMT		
					95%CI			95%CI	
Group	**Timing**	**N**	**n**	**%**	**L.L.**	**U.L.**	**value**	**L.L.**	**U.L.**
- Each HRV group									
- pooled HRV groups									
- placebo									

N = number of subjects with available data
n/% = number/percentage of subjects with concentration above the cut-off
min=minimum concentration
max=maximum concentration
95% CI, L.L and U.L = lower and upper limits of the 95% CI
Anti-PRP: cut-off = 0.15mcg/ml and 1 mcg/ml (with 3 decimals for GMT)
Anti-D: cut-off = 0.1 IU/ml (with 3 decimals for GMT)
Anti-T: cut-off = 0.1 IU/ml (with 3 decimals for GMT)
Anti-BPT: cut-off = 15 EL.U/ml (with 1 decimal for GMT)
Anti-HBs: cut-off = 10 mcg/ml (with 3 decimals for GMT)
Anti Polio type1, 2 and 3: cut-off = 8 (with 1 decimal for GMT)

Distribution of each antibody concentrations
ATP immunogenicity cohort (Total cohort, if required)

			≥limit1		≥limit2		≥ limit3		≥ limit4		≥ limit5		≥ limit6	
Group	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
- Each HRV group														
- pooled HRV groups														
- placebo														

N = number of subjects with available data
n/% = number/percentage of subjects with concentration within the specified range
The number of limits and the values of the limits is different from one antibody to another:
- for anti-Polio 1 antibody titres: 6 limits (including the cut-off): 8, 16, 32, 64, 128, 256
- for anti-Polio 2 antibody titres: 6 limits (including the cut-off): 8, 16, 32, 64, 128, 256
- for anti-Polio 3 antibody titres: 6 limits (including the cut-off): 8, 16, 32, 64, 128, 256
- for anti-PRP antibody titres: 5 limits (including the cut-off): 0.15, 0.5, 1, 5, 10 mcg/ml
- for anti-diphtheria toxoid antibody titres: 3 limits (including the cut-off): 0.1, 1, 10 IU/ml
- for anti-tetanus toxoid antibody titres: 3 limits (including the cut-off): 0.1, 1, 10 IU/ml
- for anti-HBs antibody titres: 3limits (including the cut-off): 10, 100, 1000 mcg/ml
- for anti-BPT antibody titres: 4 limits (including the cut-off): 15, 30, 60, 120 EL.U/ml

Sub-analyses for anti-polio antibodies will be performed; tables describe above will be generated for subjects who received OPV at birth and for subjects who didn't received OPV at birth.

In addition for the concomitant vaccination and OPV, reverse cumulative curve titers two months after the second dose and at the end of the first efficacy follow-up period will be displayed for the ATP immunogenicity cohort.

Difference between each vaccine group and placebo two months after dose 2 will be evaluated with respect to immune response to concomitant vaccination and OPV, and with respect to vaccine take:

- The asymptotic two-sided 95% CI for difference in seropositivity/seroprotection rates/vaccine take between each vaccine group and the placebo group will be calculated.

Difference in seropositivity/seroprotection rates two months after dose 2 between each vaccine group and the placebo group, for the concomitant vaccination and OPV- ATP immunogenicity cohort

						Difference in seropositivity/seroprotection rates (Placebo minus HRV)		
	Group	**N**	**%**	**Group**	**N**	**%**	**Value (%)**	**95 % CI L.L**	**U.L**
Anti-PRP	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-D	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-T	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-B *pertussis*	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-HBs	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-Polio 1	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-Polio 2	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-Polio 3	Placebo			*- each HRV group* *- pooled HRV groups*					

Source: Appendix III.A
Notes: N = number of subjects with available data
% = percentage of seropositive/seroprotected subjects
95% CI = asymptotic 95% confidence interval; L.L. = lower limit, U.L. = upper limit

Difference in percentage of subjects with vaccine take two months after dose 2 (calculated on combined doses) between each HRV and placebo groups - ATP immunogenicity cohort

						Difference in vaccine take (HRV minus Placebo)		
						Value	**95 % CI**	
Group	**N**	**%**	**Group**	**N**	**%**	**(%)**	**L.L**	**U.L**
- each HRV group			Placebo					
- pooled HRV groups								

Source: Appendix III.A
Notes: N = number of subjects with available data
% = percentage of subjects with vaccine take two months after dose 2
95% CI = asymptotic 95% confidence interval; L.L. = lower limit, U.L. = upper limit

- The two-sided 95% CI for the ratio of GMTs between each vaccine group and the placebo group will also be computed for the concomitant vaccination and OPV (using a one-way ANOVA model on the logarithm10 transformation of the titers).

Ratio of GMTs two months after dose 2 between each vaccine group and the placebo group, for the concomitant vaccination and OPV - ATP immunogenicity cohort

							GMTs ratio (Placebo over HHV)		
								95 % CI	
	Group	**N**	**GMT**	**Group**	**N**	**GMT**	**Value**	**L.L**	**U.L**
Anti-PRP	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-D	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-T	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-B pertussis	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-HBs	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-Polio 1	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-Polio 2	Placebo			*- each HRV group* *- pooled HRV groups*					
Anti-Polio 3	Placebo			*- each HRV group* *- pooled HRV groups*					

Source: Appendix III.A
Notes: N = number of subjects with available data
95% CI = asymptotic 95% confidence interval; L.L. = lower limit, U.L. = upper limit

Difference between each vaccine group and placebo after dose 3 at Visit 4 will also be evaluated with respect to immune response to concomitant vaccination and OPV, and with respect to vaccine take:

- The asymptotic two-sided 95% CI for difference in seropositivity/seroprotection rates/vaccine take between each vaccine group and the placebo group will be calculated.

- The two-sided 95% CI for the ratio of GMTs between each vaccine group and the placebo group will also be computed for the concomitant vaccination and

OPV (using a one-way ANOVA model on the logarithm10 transformation of the titers).

8.4.2 For the subset of subjects receiving 3 doses of HRV/placebo (Total vaccinated cohort only)

Tables 11, 12 and 15, and Supplement 10 mentioned in section 4.3. of the PjRAP will be generated this study.

For the concomitant vaccination and OPV, the following tables will be generated :

GMC and seropositivity/seroprotection rates for anti- (each vaccine antigen) antibody
Total vaccinated cohort

			≥cut-off				GMT		
					95%CI			95%CI	
Group	**Timing**	**N**	**n**	**%**	**L.L.**	**U.L.**	**value**	**L.L.**	**U.L.**
- Each HRV group									
- pooled HRV groups									
- placebo									

N = number of subjects with available data
n/% = number/percentage of subjects with concentration above the cut-off
min=minimum concentration
max=maximum concentration
95% CI, L.L and U.L = lower and upper limits of the 95% CI
Anti-PRP: cut-off = 0.15mcg/ml and 1 mcg/ml (with 3 decimals for GMT)
Anti-D: cut-off = 0.1 IU/ml (with 3 decimals for GMT)
Anti-T: cut-off = 0.1 IU/ml (with 3 decimals for GMT)
Anti-BPT: cut-off = 15 EL.U/ml (with 1 decimal for GMT)
Anti-HBs: cut-off = 10 mcg/ml (with 3 decimals for GMT)
Anti Polio type1, 2 and 3: cut-off = 8 (with 1 decimal for GMT)

Distribution of each antibody concentrations
Total vaccinated cohort

Group	Timing	N	≥limit1		≥limit2		≥ limit3		≥ limit4		≥ limit5		≥ limit6	
			n	%	n	%	n	%	n	%	n	%	n	%
- Each HRV group														
- pooled HRV groups														
- placebo														

N = number of subjects with available data
n/% = number/percentage of subjects with concentration within the specified range
The number of limits and the values of the limits is different from one antibody to another:
- for anti-Polio 1 antibody titres: 6 limits (including the cut-off): 8, 16, 32, 64, 128, 256
- for anti-Polio 2 antibody titres: 6 limits (including the cut-off): 8, 16, 32, 64, 128, 256
- for anti-Polio 3 antibody titres: 6 limits (including the cut-off): 8, 16, 32, 64, 128, 256
- for anti-PRP antibody titres: 5 limits (including the cut-off): 0.15, 0.5, 1, 5, 10 mcg/ml
- for anti-diphtheria toxoid antibody titres: 3 limits (including the cut-off): 0.1, 1, 10 IU/ml
- for anti-tetanus toxoid antibody titres: 3 limits (including the cut-off): 0.1, 1, 10 IU/ml
- for anti-HBs antibody titres: 3limits (including the cut-off): 10, 100, 1000 mcg/ml
- for anti-BPT antibody titres: 4 limits (including the cut-off): 15, 30, 60, 120 EL.U/ml

In addition, for all antigens, the distribution of antibody titers two months after the second dose (rotavirus only) and after the third dose (all antigens) will be displayed using reverse cumulative curve like in supplement 11 of the PjRAP.

8.5 List of tables and figures

Denomination	Table (figure) in the report	Suppl. Table	Working Table (figure)
Demography			
For the subset of subjects receiving 2 doses of HRV or placebo:			
Number of subjects enrolled into the study as well as the number of subjects excluded from ATP cohorts with reasons for exclusion	X		
Number of subjects at each visit and list of dropped-out subjects until Visit at one year of age - *Total cohort*			X
Counts of subjects enrolled, completed, dropped and reason for drop-out until Visit at one year of age - *Total cohort*	X		
Compliance - *Total vaccinated cohort*		X	
Deviations from specifications for age and intervals between study visits - *Total cohort*		X	
Minimum and maximum visit dates – *Total cohort*			X
Number of subjects enrolled at each center by group - *Total cohort*	X		
Summary of demographic characteristics (age calculated in weeks) - *Total vaccinated cohort*		X	
Summary of demographic characteristics (age calculated in weeks) - *ATP immunogenicity cohort*		X	
Summary of demographic characteristics (age calculated in weeks) - *ATP efficacy cohort*	X		
Summary of demographic characteristics (age calculated in weeks) in Brazil – *Total vaccinated cohort*		X	
Summary of demographic characteristics (age calculated in weeks) in Mexico - *Total vaccinated cohort*		X	
Summary of demographic characteristics (age calculated in weeks) in Venezuela - *Total vaccinated cohort*		X	
Summary of age at the second dose (calculated in weeks) - *Total vaccinated cohort*			X
Summary of age at the second dose (calculated in weeks) - *ATP immunogenicity cohort*			X
Summary of age at the second dose (calculated in weeks) - *ATP efficacy cohort*			X
Increase in height and weight from Visit 1 to Visit 4 - *Total vaccinated cohort*		X	
Percentage of subjects who received OPV at birth - *ATP immunogenicity cohort*		X	

Denomination	**Table (figure) in the report**	**Suppl. Table**	**Working Table (figure)**
Summary of feeding criteria - *ATP immunogenicity cohort*		X	
Percentage of subjects in each of the feeding criteria category used in the logisitc regression - *ATP immunogenicity cohort*			X
For the subset of subjects receiving 3 doses of HRV or placebo:			
Number of subjects enrolled into the study	X		
Number of subjects at each visit and list of dropped-out subjects until Visit at one year of age - *Total cohort*			X
Counts of subjects enrolled, completed, dropped and reason for drop-out until Visit at one year of age - *Total cohort*	X		
Compliance - *Total vaccinated cohort*		X	
Deviations from specifications for age and intervals between study visits - *Total cohort*		X	
Minimum and maximum visit dates – *Total cohort*			X
Number of subjects enrolled at each center by group - *Total cohort*	X		
Summary of demographic characteristics (age calculated in weeks) - *Total vaccinated cohort*		X	
Summary of age at the second dose (calculated in weeks) - *Total vaccinated cohort*			X
Summary of age at the third dose (calculated in weeks) - *Total vaccinated cohort*			X
Increase in height and weight from Visit 1 to Visits 5 - *Total vaccinated cohort*		X	
Percentage of subjects who received OPV at birth - *Total vaccinated cohort*		X	
Summary of feeding criteria - *Total vaccinated cohort*		X	X
<u>Reactogenicity</u>			
For all subjects, restricted to doses 1 and 2 of HRV/placebo			
Number and percentage of subjects who received vaccine dose(s) - *Total vaccinated cohort*	X		
§Percentage of doses reporting symptoms (solicited or unsolicited) during the 15-day follow-up period, for each dose - *Total vaccinated cohort*		X	
§Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15-day follow-up period, for all doses - *Total vaccinated cohort*	X		
§Percentage of doses reporting grade 3 (solicited or unsolicited) during the 15-day follow-up period, for each dose - *Total vaccinated cohort*		X	
§Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15-day follow-up period, for all doses - *Total vaccinated cohort*		X	

Denomination	**Table (figure) in the report**	**Suppl. Table**	**Working Table (figure)**
§Percentage of doses reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15-day follow-up period, for each dose - *Total vaccinated cohort*		X	
§Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the solicited 15-day follow-up period, for all doses - *Total vaccinated cohort*		X	
§Percentage of doses reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity, and those considered to be related to vaccination during the 15-day follow-up period, for each dose - *Total vaccinated cohort*		X	
§Percentage of doses and of subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity, and those considered to be related to vaccination during the 15-day follow-up period, for all doses - *Total vaccinated cohort*	X		
Statistical comparisons between groups for the percentage of subjects reporting each solicited symptom after any doses - *Total vaccinated cohort*	X		
Percentage of doses reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity, and those considered to be related to vaccination during the first 3-day and the first 8-day after vaccination, for each dose - *Total vaccinated cohort*			X
Percentage of doses and of subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity, and those considered to be related to vaccination during the first 3-day and the first 8-day after vaccination, for all doses - *Total vaccinated cohort*			X
Summary of solicited gastrointestinal symptoms (diarrhea and vomiting) and fever for subjects who reported both diarrhea and vomiting during the 15-day solicited follow-up period - *Total vaccinated cohort*		X	
Prevalence of diarrhea by day after dose 1, during the solicited follow-up period - *Total vaccinated cohort*		X	
Prevalence of diarrhea by day after dose 2, during the solicited follow-up period - *Total vaccinated cohort*		X	
Prevalence of vomiting by day after dose 1, during the solicited follow-up period - *Total vaccinated cohort*		X	
Prevalence of vomiting by day after dose 2, during the solicited follow-up period - *Total vaccinated cohort*		X	
Prevalence of fever by day after dose 1, during the solicited follow-up period - *Total vaccinated cohort*		X	
Prevalence of fever by day after dose 2, during the solicited follow-up period - *Total vaccinated cohort*		X	
Percentage of subjects with missing values for diarrhea by day, during the solicited follow-up period - *Total vaccinated cohort*			X
Percentage of subjects with missing values for vomiting by day, during the solicited follow-up period - *Total vaccinated cohort*			X
Percentage of subjects with missing values for fever by day, during the solicited follow-up period - *Total vaccinated cohort*			X
Duration (in days) of diarrhea during the solicited follow-up period - *Total vaccinated cohort*		X	

Denomination	**Table (figure) in the report**	**Suppl. Table**	**Working Table (figure)**
Duration (in days) of vomiting during the solicited follow-up period - *Total vaccinated cohort*		X	
Duration (in days) of fever during the solicited follow-up period - *Total vaccinated cohort*		X	
§The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms, from day 0 to day 42 after any vaccination - *Total vaccinated cohort*		X	
§The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from day 0 to day 42 after any vaccination - *Total vaccinated cohort*	X		
§The percentage of subjects with graded 3 unsolicited symptoms classified by WHO Preferred Terms, from day 0 to day 42 after any vaccination - *Total vaccinated cohort*	X		
§The percentage of doses with unsolicited symptoms classified by WHO Preferred Terms, from day 0 to day 42 after any vaccination - *Total vaccinated cohort*		X	
§The percentage of doses with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from day 0 to day 42 after any vaccination - *Total vaccinated cohort*		X	
§The percentage of doses with graded 3 unsolicited symptoms classified by WHO Preferred Terms, from day 0 to day 42 after any vaccination - *Total vaccinated cohort*		X	
The percentage of subjects with gastrointestinal symptoms (unsolicited symptoms), from day 0 to day 42 after any vaccination - *Total cohort*		X	
The percentage of doses with gastrointestinal symptoms (unsolicited symptoms), from day 0 to day 42 after any vaccination - *Total vaccinated cohort*		X	
Number and percentage of subjects who took at least one concomitant medication from Day 0 to Day 14 after vaccination, by type - *Total vaccinated cohort*	X		
Number and percentage of subjects who took at least one concomitant medication up to end of the first efficacy follow-up Visit, by type - *Total vaccinated cohort*			X
Percentage of subjects who took antipyretic after dose 1, by day from Day 0 to Day 42 - *Total vaccinated cohort*		X	
Percentage of subjects who took antipyretic after dose 2, by day from Day 0 to Day 42 - *Total vaccinated cohort*		X	
For the subset of subjects receiving 3 doses of HRV or placebo:			
Number and percentage of subjects who received vaccine dose(s) - *Total vaccinated cohort*	X		
Percentage of doses reporting symptoms (solicited or unsolicited) during the 15-day follow-up period, for each dose - *Total vaccinated cohort*		X	
Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) during the 15-day follow-up period, for all doses - *Total vaccinated cohort*	X		
Percentage of doses reporting grade 3 (solicited or unsolicited) during the 15-day follow-up period, for each dose - *Total vaccinated cohort*		X	

Denomination	**Table (figure) in the report**	**Suppl. Table**	**Working Table (figure)**
Percentage of doses and of subjects reporting grade 3 symptoms (solicited or unsolicited) during the 15-day follow-up period, for all doses - *Total vaccinated cohort*		X	
Percentage of doses reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the 15-day follow-up period, for each dose - *Total vaccinated cohort*		X	
Percentage of doses and of subjects reporting symptoms (solicited or unsolicited) assessed as related to vaccination during the solicited 15-day follow-up period, for all doses - *Total vaccinated cohort*		X	
Percentage of doses reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity, and those considered to be related to vaccination during the 15-day follow-up period, for each dose - *Total vaccinated cohort*		X	
Percentage of doses and of subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity, and those considered to be related to vaccination during the 15-day follow-up period, for all doses - *Total vaccinated cohort*	X		
Percentage of doses and of subjects reporting each solicited general symptoms including those graded 3 and those graded 2 or 3 in intensity, and those considered to be related to vaccination during the first 3-day and the first 8-day after vaccination, for all doses - *Total vaccinated cohort*			X
The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms, from day 0 to day 42 after any vaccination - *Total vaccinated cohort*		X	
The percentage of subjects with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from day 0 to day 42 after any vaccination - *Total vaccinated cohort*	X		
The percentage of subjects with graded 3 unsolicited symptoms classified by WHO Preferred Terms, from day 0 to day 42 after any vaccination - *Total vaccinated cohort*	X		
The percentage of doses with unsolicited symptoms classified by WHO Preferred Terms, from day 0 to day 42 after any vaccination - *Total vaccinated cohort*		X	
The percentage of doses with unsolicited symptoms classified by WHO Preferred Terms assessed as related to vaccination, from day 0 to day 42 after any vaccination - *Total vaccinated cohort*		X	
The percentage of doses with graded 3 unsolicited symptoms classified by WHO Preferred Terms, from day 0 to day 42 after any vaccination - *Total vaccinated cohort*		X	
Number and percentage of subjects who took at least one concomitant medication from Day 0 to Day 14 after vaccination, by type - *Total vaccinated cohort*	X		
For all subjects			
Subjects with serious adverse events reported up to end of the first efficacy follow-up Visit – *Total vaccinated cohort*	X		

Denomination	Table (figure) in the report	Suppl. Table	Working Table (figure)
Immunogenicity			
For the subset of subjects receiving 2 doses of HRV or placebo:			
Anti-rotavirus IgA antibody GMC and seroconversion rates - *ATP immunogenicity cohort*	X		
Anti-rotavirus IgA antibody GMC and seroconversion rates for the stool subset - *ATP immunogenicity cohort*		X	
Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies - *ATP immunogenicity cohort*	X		
Anti-rotavirus IgA antibody seroconversion rate on combined doses 1 and 2 - *ATP immunogenicity cohort*	X		
Distribution of anti-rotavirus IgA antibody concentrations - *ATP immunogenicity cohort*		X	
Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations two months after dose 2 - *ATP immunogenicity cohort*		X	
Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations at the end of the first efficacy follow-up period - *ATP immunogenicity cohort*		X	
Number of subjects with vaccine virus in stool samples collected after each dose at pre-determined time points, for the stool subset - *ATP immunogenicity cohort*	X		
Number of subjects with vaccine virus in gastroenteritis stool samples collected up to Visit 3, for the stool subset - *ATP immunogenicity cohort*	X		
Percentage of subjects with vaccine take after each dose, for the stool subset - *ATP immunogenicity cohort*	X		
Percentage of subjects with vaccine take after combined doses 1 and 2, for the stool subset - *ATP immunogenicity cohort*	X		
GMC and seropositivity/seroprotection rates for anti (each concomitant vaccine and OPV antigen) antibody - *ATP immunogenicity cohort*	X		
GMC and seropositivity/seroprotection rates for anti (each OPV antigen) antibody for the subset of subjects who received OPV at birth - *ATP immunogenicity cohort*		X	
GMC and seropositivity/seroprotection rates for anti (each OPV antigen) antibody for the subset of subjects who didn't received OPV at birth - *ATP immunogenicity cohort*		X	
Distribution of each concomitant and OPV antibody concentrations - *ATP immunogenicity cohort*		X	
Distribution of each OPV antibody concentrations for the subset of subjects who received OPV at birth - *ATP immunogenicity cohort*		X	
Distribution of each OPV antibody concentrations for the subset of subjects who didn't received OPV at birth - *ATP immunogenicity cohort*		X	
Reverse cumulative distribution curves for anti- (each concomitant vaccine and OPV antigen) two months after dose 2 - *ATP immunogenicity cohort*		X	
Reverse cumulative distribution curves for anti- (each concomitant vaccine and OPV antigen) the end of the first efficacy follow-up period - *ATP immunogenicity cohort*		X	

Denomination	**Table (figure) in the report**	**Suppl. Table**	**Working Table (figure)**
Difference in seropositivity/seroprotection rates two months after dose 2 between each vaccine group and the placebo group, for the concomitant vaccination and OPV - *ATP immunogenicity cohort*	X		
Difference in percentage of subjects with vaccine take two months after dose 2 between each HRV and placebo groups - *ATP immunogenicity cohort*	X		
Ratio of GMTs two months after dose 2 between each vaccine group and the placebo group, for the concomitant vaccination and OPV- *ATP immunogenicity cohort*	X		
Difference in seropositivity/seroprotection rates at Visit 4 between each vaccine group and the placebo group, for the concomitant vaccination and OPV - *ATP immunogenicity cohort*		X	
Ratio of GMTs at Visit 4 between each vaccine group and the placebo group, for the concomitant vaccination and OPV- *ATP immunogenicity cohort*		X	
For the subset of subjects receiving 3 doses of HRV or placebo:			
Anti-rotavirus IgA antibody GMC and seroconversion rates - *Total vaccinated cohort*	X		
Anti-rotavirus IgA antibody GMC calculated on subjects seropositive for anti-rotavirus IgA antibodies - *Total vaccinated cohort*	X		
Distribution of anti-rotavirus IgA antibody concentrations - *Total vaccinated cohort*		X	
Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations two months after dose 2 - *Total vaccinated cohort*		X	
Reverse cumulative distribution curves for anti-rotavirus IgA antibody concentrations two months after dose 3 - *Total vaccinated cohort*		X	
Number of subjects with vaccine virus in stool samples collected at pre-determined time points, for the stool subset - *Total vaccinated cohort*	X		
GMC and seropositivity/seroprotection rates for Anti (each concomitant vaccine and OPV antigen) antibody - *Total vaccinated cohort*	X		
Distribution of each concomitant and OPV antibody concentrations *Total vaccinated cohort*		X	
Reverse cumulative distribution curves for anti- (each concomitant vaccine and OPV antigen) two months after dose 3 - *Total vaccinated cohort*		X	
<u>Efficacy</u>			
For the subset of subjects receiving 2 doses of HRV or placebo:			
Percentage of subjects with vaccine virus in gastroenteritis stool samples collected up to visit 3 – *Total vaccinated cohort*		X	
Number and percentage of subjects who reported gastroenteritis episode(s) during the first efficacy follow-up period – *ATP efficacy cohort*		X	
Number of gastroenteritis episodes with no available stool results during the first efficacy follow-up period - *ATP efficacy cohort*			X

Denomination	**Table (figure) in the report**	**Suppl. Table**	**Working Table (figure)**
Number of gastroenteritis episodes and rotavirus gastroenteritis episodes reported during the first efficacy follow-up period, by severity - *ATP efficacy cohort*	X		
Percentage of subjects with rotavirus gastroenteritis episodes reported during the first efficacy follow-up period, by serotype - *ATP efficacy cohort*	X		
Number of rotavirus gastroenteritis episodes reported during the first efficacy follow-up period, by serotype - *ATP efficacy cohort*			X
Characteristics of rotavirus gastroenteritis episodes reported during the first efficacy follow-up period, by serotype and overall - *ATP efficacy cohort*		X	
Duration (in year) of the follow-up periods for the first efficacy period - *ATP efficacy cohort*		X	
Percentage of rotavirus gastroenteritis episodes with mixed infections during the first efficacy follow-up period - ATP efficacy cohort		X	
Percentage of subjects reporting any rotavirus gastroenteritis episode and efficacy of the vaccine during the first efficacy follow-up period - *ATP efficacy cohort*	X		
Percentage of subjects reporting any pure rotavirus gastroenteritis episode and efficacy of the vaccine during the first efficacy follow-up period - *ATP efficacy cohort*	X		
Percentage of subjects reporting any mixed rotavirus gastroenteritis episode and efficacy of the vaccine during the first efficacy follow-up period - *ATP efficacy cohort*	X		
Percentage of subjects reporting severe rotavirus gastroenteritis episode and efficacy of the vaccine during the first efficacy follow-up period - *ATP efficacy cohort*	X		
Percentage of subjects reporting severe pure rotavirus gastroenteritis episode and efficacy of the vaccine during the first efficacy follow-up period - *ATP efficacy cohort*	X		
Percentage of subjects reporting severe mixed rotavirus gastroenteritis episode and efficacy of the vaccine during the first efficacy follow-up period - *ATP efficacy cohort*	X		
Percentage of subjects reporting any rotavirus gastroenteritis episode and efficacy of the vaccine during the first efficacy follow-up period, by serotype - *ATP efficacy cohort*		X	
Percentage of subjects reporting severe rotavirus gastroenteritis episode and efficacy of the vaccine during the first efficacy follow-up period, by serotype - *ATP efficacy cohort*		X	
Percentage of subjects in the HRV vaccine group reporting rotavirus GE during the first efficacy follow-up period, by status of anti-rotavirus IgA antibody concentration two months after Dose 2 - *ATP efficacy cohort*		X	
Percentage of subjects hospitalized for gastroenteritis and efficacy of the vaccine during the first efficacy follow-up periods - *ATP efficacy cohort*		X	
Percentage of subjects hospitalized for rotavirus gastroenteritis and efficacy of the vaccine during the first efficacy follow-up periods - *ATP efficacy cohort*		X	

Denomination	Table (figure) in the report	Suppl. Table	Working Table (figure)
For the subset of subjects receiving 3 doses of HRV or placebo:			
Percentage of subjects reporting any rotavirus gastroenteritis from 2 weeks after Dose 3 till end of the first efficacy follow-up period – *Total vaccinated cohort*	X		
Percentage of subjects reporting severe rotavirus gastroenteritis from 2 weeks after Dose 3 till end of the first efficacy follow-up period - *Total vaccinated cohort*	X		
Percentage of subjects reporting any rotavirus gastroenteritis from day of Dose 1 till end of the first efficacy follow-up period - *Total vaccinated cohort*		X	
Percentage of subjects reporting severe rotavirus gastroenteritis from day of Dose 1 till end of the first efficacy follow-up period - *Total vaccinated cohort*		X	

Notes:
[§] will also be generated by country
For immunogenicity analysis, the tables for the *Total vaccinated cohort* are done only if the percentage of excluded subjects with available post-vaccination results from the ATP immunogenicity cohort exceeds 5 %.
For safety analysis, the tables for the *ATP cohort* are done only if the percentage of excluded subjects from the ATP safety cohort exceeds 5 %. **The ATP tables will be limited to those marked [§]**
The analyses of safety, immunogenicity and efficacy for the subset of subjects who received 3 doses of HRV or placebo will only be performed on the total vaccinated cohort
All the tables defined above for the efficacy analysis are also performed on the Total vaccinated cohort.
For the analysis of efficacy after Dose 1 for the subset of subjects receiving 2 doses of HRV/placebo, all efficacy tables for the first efficacy follow-up period will also be performed (as supplements) for subjects with efficacy follow-up data available after dose 1 (efficacy follow-up is dereived from any contact after the first dose of HRV vaccine or placebo).

9 Annex Analysis

Analysis of data from the end of the first efficacy follow-up period till the end of the second efficacy follow-up period and efficacy analyses on both efficacy follow-up periods will be presented in an annex.

9.1 Study cohorts and demography analysis

All the following tables mentioned in section 4.1. of the PjRAP will be generated for this annex, separately for the subset of subjects receiving 2 doses of HRV vaccine or placebo and for the subset of subjects receiving 3 doses of HRV vaccine or placebo. :

- Table 1
- Table 2
- Table 4 for subjects entered into the surveillance period of the second efficacy period
- Supplement 2 restricted to Visit 4 and Visit 5,
- Working Table 1 restricted to Visit 4 and Visit 5,
- Working Table 2 restricted to Visit 5.

In this annex, end of the second efficacy follow-up visit is as follows:

- Intervals between study visits for the subset of subjects receiving 2 doses of study vaccine/placebo will be as follows

Interval	Protocol intervals	Adapted intervals
First efficacy follow-up visit → Second efficacy follow-up visit	Brazil & Venezuela: 335–395 days Mexico: June 1 -> 30, 2003 (after the end of rotavirus season)	No subjects will be eliminated for not respecting the time interval between Visits 4 and 5

- Intervals between study visits for the subset of subjects receiving 3 doses of study vaccine/placebo will be as follows

Interval	Protocol intervals	Adapted intervals
First efficacy follow-up visit → Second efficacy follow-up visit	Brazil & Venezuela: 335–395 days Mexico: June 1 -> 30, 2003 (after the end of rotavirus season)	No subjects will be eliminated for not respecting the time interval between Visits 5 and 6

In addition, the weight and height increase from visit 1 will be summarized by group for all Visits, as in the following tables :

Increase in height and weight from Visit 1 to Visit 5, for the subset of subjects receiving 2 doses of study vaccine/placebo (Total vaccinated cohort)

Visit	**Characteristics**	**Parameters or Categories**	**Each Group (N =XXX) Value**	**Total (N =XXX) Value**
	Increase in height (cm) from Visit 1	Mean SD Median Unknown		
	Increase in weight (kg) from Visit 1	Mean SD Median Unknown		

N= total number of subjects in the considered cohort, by group or in total (sum for all groups)
Value = value of the considered parameter
SD= standard deviation

Increase in height and weight from Visit 1 to Visit 6 for the subset of subjects receiving 3 doses of study vaccine/placebo (Total vaccinated cohort)

Visit	**Characteristics**	**Parameters or Categories**	**Each Group (N =XXX) Value**	**Total (N =XXX) Value**
	Increase in height (cm) from Visit 1	Mean SD Median Unknown		
	Increase in weight (kg) from Visit 1	Mean SD Median Unknown		

N= total number of subjects in the considered cohort, by group or in total (sum for all groups)
Value = value of the considered parameter
SD= standard deviation

9.2 Efficacy analysis

9.2.1 Subset of subjects receiving 2 doses of HRV vaccine or placebo

All the tables mentioned in section 4.4. of the PjRAP, except Supplement 12, will be generated for the subset of subjects entered into the surveillance period of the second efficacy period. Three country (=geographical areas in the PjRAP) are considered : Brazil, Mexico and Venezuela.

In each of these tables, pooled data from the three HRV groups will also be included.

In addition, the efficacy of HRV against hospitalization for rotavirus gastroenteritis will be computed and presented as in Table 22 of the PjRAP.

9.2.2 Subset of subjects receiving 3 doses of HRV vaccine or placebo (Total vaccinated cohort only)

The following Tables will be generated :

*Percentage of subjects reporting any (**severe**) rotavirus gastroenteritis during the second efficacy follow-up period - Total vaccinated cohort*

Country	**Group**	**N**	**n**	**n / N**	
				rate	**95%CI**
(each area)	*- each HRV group* *- pooled HRV groups* *- placebo*				
All	*- each HRV group* *- pooled HRV groups* *- placebo*				

N = number of subjects included in each group
n = number of subjects reporting at least one rotavirus gastroenteritis episode in each group
n/N= percentage of subjects reporting at least one rotavirus gastroenteritis episode in each group
95%CI= 95%confidence intervals

*Percentage of subjects reporting any (**severe**) rotavirus gastroenteritis from 2 weeks after Dose 3 till end of the second efficacy follow-up period - Total vaccinated cohort*

Country	**Group**	**N**	**n**	**n / N** rate	95%CI
(each area)	*- each HRV group* *- pooled HRV groups* *- placebo*				
All	*- each HRV group* *- pooled HRV groups* *- placebo*				

N = number of subjects included in each group
n = number of subjects reporting at least one rotavirus gastroenteritis episode in each group
n/N= percentage of subjects reporting at least one rotavirus gastroenteritis episode in each group
95%CI= 95%confidence intervals

*Percentage of subjects reporting any (**severe**) rotavirus gastroenteritis from day of Dose 1 till end of the second efficacy follow-up period - Total vaccinated cohort*

Country	**Group**	**N**	**n**	**n / N** rate	95%CI
(each country)	*- each HRV group* *- pooled HRV groups* *- placebo*				
All	*- each HRV group* *- pooled HRV groups* *- placebo*				

N = number of subjects included in each group
n = number of subjects reporting at least one rotavirus gastroenteritis episode in each group
n/N= percentage of subjects reporting at least one rotavirus gastroenteritis episode in each group
95%CI= 95%confidence intervals

9.3 Reactogenicity / Safety analysis

The number of subjects reporting serious adverse events (SAEs) from the end of the first efficacy follow-up visit to the end of the second efficacy follow-up visit will be presented per group as in Table 9 of the PjRAP.

9.4 List of tables and figures

Denomination	Table (figure) in the report	Suppl. Table	Working Table (figure)
Demography			
For the subset of subjects receiving 2 doses of HRV or placebo and entered in the second efficacy follow-up:			
Number of subjects enrolled into the study as well as the number of subjects excluded from ATP cohorts with reasons for exclusion	X		
Number of subjects at each visit and list of dropped-out subjects - *Total cohort*			X
Counts of subjects enrolled, completed, dropped and reason for drop-out - *Total cohort*	X		
Deviations from specifications for intervals between the end of each efficacy follow-up visits - *Total cohort*		X	
Minimum and maximum visit dates – *Total cohort*			X
Summary of demographic characteristics (age calculated in weeks) - *Total vaccinated cohort*		X	
Summary of demographic characteristics (age calculated in weeks) – *ATP efficacy cohort*	X		
Increase in height and weight from Visit 1 to Visit 5 - *Total vaccinated cohort*		X	
For the subset of subjects receiving 3 doses of HRV or placebo and entered in the second efficacy follow-up:			
Number of subjects at each visit and list of dropped-out subjects - *Total cohort*			X
Counts of subjects enrolled, completed, dropped and reason for drop-out - *Total cohort*	X		
Deviations from specifications for intervals between the end of each efficacy follow-up visits - *Total cohort*		X	
Minimum and maximum visit dates – *Total cohort*			X
Summary of demographic characteristics (age calculated in weeks) - *Total vaccinated cohort*		X	
Increase in height and weight from Visit 1 to Visit 6 - *Total vaccinated cohort*		X	
Reactogenicity			
Subjects with serious adverse events reported from the end of the first efficacy follow-up visit to the end of the second efficacy follow-up visit – *Total vaccinated cohort*	X		
Efficacy			
For the subset of subjects receiving 2 doses of HRV or placebo and entered in the second efficacy follow-up:			
Number and percentage of subjects who reported gastroenteritis episode(s) results during the second efficacy follow-up period – *ATP efficacy cohort*		X	
Number and percentage of subjects who reported gastroenteritis episode(s) on combined efficacy follow-up periods – *ATP efficacy cohort*		X	

Denomination	**Table (figure) in the report**	**Suppl. Table**	**Working Table (figure)**
Number of gastroenteritis episodes with no available stools results during the second efficacy follow-up period - *ATP efficacy cohort*			X
Number of gastroenteritis episodes with no available stools results on combined efficacy follow-up periods - *ATP efficacy cohort*			X
Number of gastroenteritis episodes and rotavirus gastroenteritis episodes reported during the second efficacy follow-up period, by severity - *ATP efficacy cohort*	X		
Number of gastroenteritis episodes and rotavirus gastroenteritis episodes reported on combined efficacy follow-up periods, by severity - *ATP efficacy cohort*		X	
Percentage of subjects with rotavirus gastroenteritis episodes reported during the second efficacy follow-up period, by serotype - *ATP efficacy cohort*	X		
Percentage of subjects with rotavirus gastroenteritis episodes reported on combined efficacy follow-up periods, by serotype - *ATP efficacy cohort*		X	
Number of rotavirus gastroenteritis episodes reported during the second efficacy follow-up period, by serotype - *ATP efficacy cohort*			X
Number of rotavirus gastroenteritis episodes reported on combined efficacy follow-up periods, by serotype - *ATP efficacy cohort*			X
Characteristics of rotavirus gastroenteritis episodes reported during the second efficacy follow-up period, by serotype and overall - *ATP efficacy cohort*		X	
Characteristics of rotavirus gastroenteritis episodes reported on combined efficacy follow-up periods, by serotype and overall - *ATP efficacy cohort*		X	
Duration (in year) of the follow-up periods for the second efficacy period and on combined efficacy periods- *ATP efficacy cohort*		X	
Percentage of subjects reporting any rotavirus gastroenteritis and efficacy of the vaccine during the second efficacy follow-up period - *ATP efficacy cohort*	X		
Percentage of subjects reporting any rotavirus gastroenteritis and efficacy of the vaccine on combined efficacy follow-up periods - *ATP efficacy cohort*	X		
Percentage of subjects reporting severe rotavirus gastroenteritis and efficacy of the vaccine during the second efficacy follow-up period - *ATP efficacy cohort*	X		
Percentage of subjects reporting severe rotavirus gastroenteritis and efficacy of the vaccine on combined efficacy follow-up periods - *ATP efficacy cohort*	X		
Percentage of subjects reporting any rotavirus gastroenteritis and efficacy of the vaccine during the second follow-up period, by serotype - *ATP efficacy cohort*		X	
Percentage of subjects reporting any rotavirus gastroenteritis and efficacy of the vaccine on combined follow-up periods, by serotype - *ATP efficacy cohort*		X	
Percentage of subjects reporting severe rotavirus gastroenteritis and efficacy of the vaccine during the second follow-up period, by serotype - *ATP efficacy cohort*		X	
Percentage of subjects reporting severe rotavirus gastroenteritis and efficacy of the vaccine on combined follow-up periods, by serotype - *ATP efficacy cohort*		X	

Denomination	**Table (figure) in the report**	**Suppl. Table**	**Working Table (figure)**
Percentage of subjects hospitalized for gastroenteritis and efficacy of the vaccine during the second follow-up period - *ATP efficacy cohort*		X	
Percentage of subjects hospitalized for gastroenteritis and efficacy of the vaccine on combined efficacy follow-up periods - *ATP efficacy cohort*		X	
Percentage of subjects hospitalized for rotavirus gastroenteritis and efficacy of the vaccine during the second efficacy follow-up period - *ATP efficacy cohort*		X	
Percentage of subjects hospitalized for rotavirus gastroenteritis and efficacy of the vaccine on combined efficacy follow-up periods - *ATP efficacy cohort*		X	
Percentage of subjects in the HRV vaccine group reporting rotavirus GE on combined efficacy follow-up periods, by status of anti-rotavirus IgA antibody concentration after Dose 2 - *ATP efficacy cohort*		X	
For the subset of subjects receiving 3 doses of HRV or placebo and entered in the second efficacy follow-up:			
Percentage of subjects reporting any rotavirus gastroenteritis during the second efficacy follow-up period – *Total vaccinated cohort*	X		
Percentage of subjects reporting any rotavirus gastroenteritis from 2 weeks after Dose 3 till end of the second efficacy follow-up period – *Total vaccinated cohort*	X		
Percentage of subjects reporting any rotavirus gastroenteritis from day of Dose 1 till end of the second efficacy follow-up period - *Total vaccinated cohort*		X	
Percentage of subjects reporting severe rotavirus gastroenteritis during the second efficacy follow-up period – *Total vaccinated cohort*	X		
Percentage of subjects reporting severe rotavirus gastroenteritis from 2 weeks after Dose 3 till end of the second efficacy follow-up period – *Total vaccinated cohort*	X		
Percentage of subjects reporting severe rotavirus gastroenteritis from day of Dose 1 till end of the second efficacy follow-up period - *Total vaccinated cohort*		X	

Notes:

All the tables defined above for the efficacy analysis are also performed on the Total vaccinated cohort.

The analyses of efficacy for the subset of subjects who received 3 doses of HRV or placebo will only be performed on the total vaccinated cohort

For the analysis of second efficacy follow-up period, all the efficacy tables will also be performed (as working tables) for subjects included in the ATP efficacy cohort (second efficacy follow-up period) who had no rotavirus other than vaccine strain in stool samples collected in case of GE episode during the first efficacy follow-up period.

For the analysis of efficacy after Dose 1 for the subset of subjects receiving 2 doses of HRV/placebo and entered in the second efficacy follow-up, all efficacy tables for combined efficacy follow-up periods will also be performed (as supplements) for subjects with efficacy follow-up data available after dose 1 (efficacy follow-up is dereived from any contact after the first dose of HRV vaccine or placebo).

References

Ref 1: Santner TJ, Snell MK (1980) Small-sample confidence intervals for p1 – p2 and p1/p2 in 2x2 contingency tables, JAMA, 75: 386-394

Ref 2: Newcombe R.G. (1998) Interval estimation for difference between independent proportions: comparison of eleven methods (method 3= asymptotic standardized, method 8=Santner and Snell), Stat in Medicine, 17, 873-890

Ref 3: Proc StatXact 5 For SAS Users (2002), User Manual, Cytel Software Corporation (section 14, pp 265-326)

Ref 4: Miettinen, O. & Nurminen, M. (1985) comparative analysis of two rates, Stat in Medicine, 4, 213-266

Ref 5: Chan, I. S. F. and Zhang, Z. (1999) Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics 55, 1201-1209.

GlaxoSmithKline Biologicals
Clinical Research and Development

Clinical Study Report Approval form

Report number: 444563/006

Study title: A phase IIb, double-blind, randomized, placebo-controlled study to assess the efficacy, immunogenicity, reactogenicity and safety of two doses of GlaxoSmithKline (GSK) Biologicals' live attenuated human rotavirus (HRV) vaccine at different virus concentrations ($10^{4.7}$, $10^{5.2}$ and $10^{5.8}$ ffu) in healthy infants (approximately 2 months of age at first dose) following a 0, 2 month schedule and previously uninfected with HRV, when administered concurrently with DTPw-HBV and Hib vaccines.

Report prepared by:

[redacted] [redacted] 14 NOV 2003

Scientific Writer

Report reviewed by:

[redacted] [redacted] 14 Nov 2003

Biometrician

[redacted] [redacted] 14 Nov 2003

Clinical Study Management

[redacted] [redacted] 14/Nov 2003

Manager, Clinical Development Rotavirus Vaccin

Report accepted and approved by:

[redacted] [redacted]

Director, Clinical Development Rotavirus Vaccines

14/11/2003

Signature/ Date